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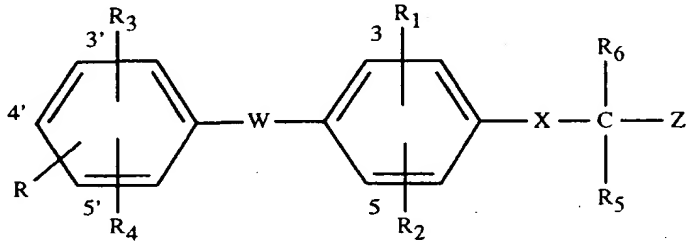
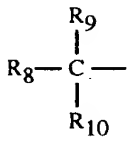
(54) Oxamic acid derivatives as hypocholesteremic agents.

(57) Disclosed are compounds of formula



(I)

wherein
R is hydrogen, hydroxy, esterified hydroxy or etherified hydroxy ;
R_1 is hydrogen, halogen, trifluoromethyl or lower alkyl ;
R_2 is hydrogen, halogen, trifluoromethyl or lower alkyl ;
R_3 is halogen, trifluoromethyl, lower alkyl, aryl, aryl-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl ; or
R_3 is the radical



wherein R_8 is hydrogen, lower alkyl, aryl, cycloalkyl, aryl-lower alkyl or cycloalkyl-lower alkyl ; R_9 is hydroxy or acyloxy ; R_{10} represents hydrogen or lower alkyl ; or R_9 and R_{10} together represent oxo ;
R_4 is hydrogen, halogen, trifluoromethyl or lower alkyl ;
X is $-NR_7$;
W is O or S ;
R_5 and R_6 together represent oxo ;
R_7 represents hydrogen or lower alkyl ;
Z represents carboxyl, carboxyl derivatized as a pharmaceutically acceptable ester or as a pharmaceutically acceptable amide ; and pharmaceutically acceptable salts thereof ; which are useful as hypocholesteremic agents.

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Summary of the Invention

The invention relates to the heteroacetic acid derivatives as defined herein which are particularly useful as potent lipid lowering agents, methods for preparation thereof, pharmaceutical compositions comprising said compounds, and a method of treating hyperlipidemia, in particular hypercholesterolemia and related conditions in mammals, by administering said compounds or pharmaceutical compositions comprising said compounds.

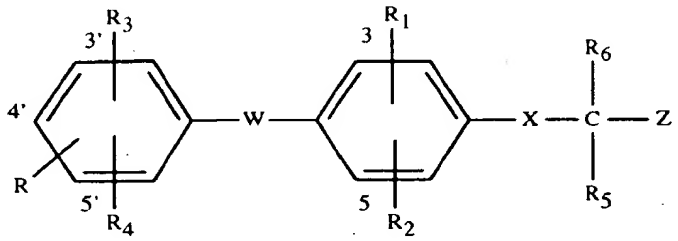
The compounds of the invention are selective thyromimetic hypolipidemic agents which enhance the clearance of cholesterol from the circulation, particularly the clearance of cholesterol in the form of low density lipoproteins (LDL). They, inter alia, upregulate (increase) hepatic LDL receptor function in mammals.

Thus, the compounds of the instant invention are primarily useful for reducing total cholesterol plasma levels in mammals, in particular for reducing levels of LDL-cholesterol.

The compounds of the invention are therefore expected to be useful for the prevention and/or treatment of occlusive cardiovascular conditions in which hyperlipidemia and hyperlipoproteinemia are implicated, such as atherosclerosis and coronary heart disease (myocardial infarctions) in mammals.

Detailed Description of the Invention

More particularly, the invention relates to the compounds of formula I



(I)

wherein

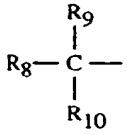
R is hydrogen, hydroxy, esterified hydroxy or etherified hydroxy;

R_1 is hydrogen, halogen, trifluoromethyl or lower alkyl;

R_2 is hydrogen, halogen, trifluoromethyl or lower alkyl;

R_3 is halogen, trifluoromethyl, lower alkyl aryl, aryl-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl; or

R_3 is the radical



(a)

wherein R_8 is hydrogen, lower alkyl, aryl, cycloalkyl, aryl-lower alkyl or cycloalkyl-lower alkyl; R_9 is hydroxy or acyloxy; R_{10} represents hydrogen or lower alkyl; or R_9 and R_{10} together represent oxo;

R_4 is hydrogen, halogen, trifluoromethyl or lower alkyl;

X is $-NR_7$;

W is O or S;

R_5 and R_6 together represent oxo;

R_7 represents hydrogen or lower alkyl;

Z represents carboxyl, carboxyl derivatized as a pharmaceutically acceptable ester or as a pharmaceutically acceptable amide; and pharmaceutically acceptable salts thereof.

Particular embodiments of the invention relate to the compounds of formula I wherein

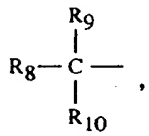
(a) R is located at the 4'-position; R1 and R_2 are located at the 3 and 5 positions, and R_3 and R_4 are located at the 3' and 5'-positions;

(b) W represents O;

(c) R_4 is hydrogen;

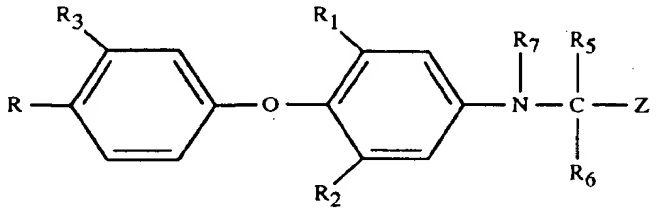
(d) R is hydroxy, esterified hydroxy or etherified hydroxy;

(e) Z is carboxyl or carboxyl esterified as a pharmaceutically acceptable ester;
(f) R_3 represents the radical



lower alkyl, aryl-lower alkyl or cycloalkyl-lower alkyl.

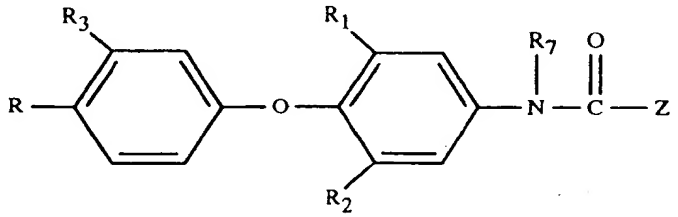
A preferred embodiment of the invention relates to the compounds of formula II



(II)

wherein R is hydroxy, esterified hydroxy or etherified hydroxy; R_1 and R_2 independently represent hydrogen, halogen, trifluoromethyl or C_1-C_3alkyl; R_3 represents lower alkyl, lower alkanoyl, hydroxy-lower alkyl, carbocyclic arylmethyl, carbocyclic aroyl or carbocyclic aryl-hydroxymethyl; R_5 and R_6 together represent oxo; R_7 represents hydrogen or lower alkyl; and Z represents carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester or amide; and pharmaceutically acceptable salts thereof.

A further preferred embodiment relates to the compounds of formula III



(III)

wherein R is hydroxy, esterified hydroxy or etherified hydroxy; R_1 represents hydrogen, halogen, trifluoromethyl or C_1-C_3alkyl; R_2 represents halogen, trifluoromethyl or C_1-C_3alkyl; R_3 represents lower alkyl, carbocyclic aroyl, carbocyclic arylmethyl or carbocyclic aryl-hydroxymethyl; R_7 represents hydrogen or lower alkyl; Z represents carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; and pharmaceutically acceptable salts thereof.

Advantageously Z represents carboxyl or carboxyl esterified as a pharmaceutically acceptable ester, preferably Z represents lower alkoxycarbonyl, e.g. C_1-C_4-alkoxy-carbonyl.

Preferred are said compounds of formula III wherein R is hydroxy, lower alkanoyloxy, lower alkoxy or tetrahydropyranyloxy; R_1 and R_2 are advantageously identical and represent halogen or C_1-C_3-alkyl; R_3 represents C_1-C_3-alkyl or monocyclic carbocyclic arylmethyl; R_7 is hydrogen or C_1-C_2-alkyl; Z is carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; and pharmaceutically acceptable salts thereof.

A further preferred embodiment relates to compounds of formula III wherein R is hydroxy, lower alkanoyloxy, lower alkoxy or tetrahydropyranyloxy; R_1 and R_2 are advantageously identical and represent halogen or C_1-C_3-alkyl; R_3 is carbocyclic aroyl or carbocyclic aryl-hydroxymethyl; R_7 is hydrogen or C_1-C_2-alkyl; Z is carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; and pharmaceutically acceptable salts thereof.

Further preferred are said compounds of formula III wherein R is hydroxy; R_1 and R_2 are advantageously identical and represent chloro or methyl; R_3 is isopropyl, benzyl or benzyl substituted by halogen, lower alkyl, lower alkoxy or trifluoromethyl; R_7 is hydrogen; Z is carboxyl or lower alkoxycarbonyl; and pharmaceutically acceptable salts thereof.

Particularly preferred are compounds of formula III wherein R is hydroxy; R_1 and R_2 are identical and rep-

resent C_1-C_3-alkyl, such as methyl, or halogen, such as chloro or bromo; R_3 represents (a) phenyl-hydroxymethyl or phenyl-hydroxymethyl substituted on phenyl by halogen, lower alkyl, lower alkoxy or trifluoromethyl; or (b) benzoyl or benzoyl substituted by halogen, lower alkyl, lower alkoxy or trifluoromethyl; or (c) C_1-C_3-alkyl, such as isopropyl; R_7 is hydrogen; and Z represents carboxy or C_1-C_4-alkoxy-carbonyl; and pharmaceutically acceptable salts thereof.

Particularly preferred are compounds of formula III wherein R is hydroxy; R_1 and R_2 are identical and represent C_1-C_3-alkyl, such as methyl, or halogen, such as chloro or bromo; R_3 represents (a) phenyl-hydroxymethyl substituted on phenyl by halogen, such as fluoro or chloro; or (b) benzoyl substituted by halogen, such as fluoro or chloro; or (c) C_1-C_3-alkyl, such as isopropyl; R_7 is hydrogen; and Z represents carboxy or C_1-C_4-alkoxy-carbonyl; and pharmaceutically acceptable salts thereof.

Particularly preferred are compounds of formula III wherein R is hydroxy; R_1 and R_2 are identical and represent chloro or methyl; R_3 is phenyl-hydroxymethyl or phenyl-hydroxymethyl substituted on phenyl by halogen, lower alkyl, lower alkoxy or trifluoromethyl; R_7 is hydrogen; Z is carboxyl or lower alkoxycarbonyl; and pharmaceutically acceptable salts thereof.

Particularly preferred are compounds of formula III wherein R is hydroxy; R_1 and R_2 are identical and represent C_1-C_3-alkyl, such as methyl, or halogen, such as chloro or bromo; R_3 is (a) 4-halo-phenyl-hydroxymethyl, especially in which halo represents fluoro or chloro; or (b) C_1-C_3-alkyl, especially isopropyl; R_7 is hydrogen; and Z represents carboxy or C_1-C_4-alkoxy-carbonyl; and pharmaceutically acceptable salts thereof.

Certain compounds of the invention which have one or more asymmetric centers can exist in the form of racemates, enantiomers and mixtures thereof, all of which are within the scope of the invention.

The definitions used herein, unless denoted otherwise, have the following meanings within the scope of the present invention.

Aryl represents carbocyclic or heterocyclic aryl.

Carbocyclic aryl represents optionally substituted phenyl or optionally substituted naphthyl.

Optionally substituted phenyl represents preferably phenyl or phenyl substituted by one to three substituents, such being advantageously lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, halogen, cyano, trifluoromethyl, lower alkanoylamino or lower alkoxycarbonyl.

Optionally substituted naphthyl represents 1- or 2-naphthyl or 1- or 2-naphthyl preferably substituted by lower alkyl, lower alkoxy or halogen.

Heterocyclic aryl represents preferably monocyclic heterocyclic aryl such as optionally substituted thienyl, furanyl, pyridyl, pyrrolyl or N-lower alkylpyrrolyl.

Optionally substituted furanyl represents 2- or 3-furanyl or 2- or 3-furanyl preferably substituted by lower alkyl.

Optionally substituted pyridyl represents 2-, 3- or 4-pyridyl or 2-, 3- or 4-pyridyl preferably substituted by lower alkyl or halogen.

Optionally substituted thienyl represents 2- or 3-thienyl or 2- or 3-thienyl preferably substituted by lower alkyl.

Optionally substituted pyrrolyl or N-lower alkylpyrrolyl, respectively, represent 2- or 3-pyrrolyl or N-lower alkyl-2- or -3-pyrrolyl or represent or 2- or 3-pyrrolyl or N-lower alkyl-2- or -3-pyrrolyl prefereably substituted by lower alkyl.

Aryl as in aryl-lower and the like is preferably phenyl or phenyl substituted by one or two of lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen, trifluoromethyl, cyano, lower alkanoylamino or lower alkoxycarbonyl.

Aryl-lower alkyl is advantageously benzyl or phenethyl optionally substituted by one or two of lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen or trifluoromethyl.

Esterified hydroxy represents acyloxy, e.g. acyloxy derived from an organic carboxylic acid, preferably lower alkanoyloxy, aroyloxy, or aryl-lower alkanoyloxy; also 3,7,12(3α,5β,7α,12α)-trihydroxy-cholan-24-oyloxy (derived from cholic acid), and the like.

Etherified hydroxy represents preferably lower alkoxy, lower alkenyloxy, C_5-C_7-cycloalkyloxy, carbocyclic aryl-lower alkoxy, tetrahydropyranyloxy, C5-C_7-cycloalkyl-lower alkoxy, and the like.

Carboxyl derivatized as a pharmaceutically acceptable ester represents esterified carboxyl, advantageously a prodrug ester that may be convertible by solvolysis or under physiological conditions to the free carboxylic acid, such being preferably lower alkoxycarbonyl; (amino, acylamino, mono- or di-lower alkylamino)-lower alkoxycarbonyl; carboxy- lower alkoxycarbonyl, e.g. alpha-carboxy-lower alkoxycarbonyl; lower alkoxy-carbonyl-lower alkoxycarbonyl, e.g. alpha-lower alkoxycarbonyl-lower alkoxycarbonyl; α-(di-lower alkylamino, amino, mono-lower alkylamino, morpholino, piperidino, pyrrolidino, 1-lower alkyl-piperazino)-carbonyl-lower alkoxycarbonyl; carbocyclic or heterocyclic aryl-lower alkoxycarbonyl, preferably optionally (halo, lower alkyl or lower alkoxy)-substituted benzyloxycarbonyl, or pyridylmethoxycarbonyl; 1-(hydroxy, lower alkanoyloxy or

lower alkoxy)-lower alkoxycarbonyl, e.g. pivaloyloxymethoxycarbonyl; (hydroxy, lower alkanoyloxy or lower alkoxy)-lower alkoxymethoxycarbonyl; 1-(lower alkoxycarbonyloxy)-lower alkoxycarbonyl; 5-indanyloxycarbonyl; 3-phthalidoxycarbonyl and (lower alkyl, lower alkoxy or halo)-substituted 3-phthalidoxycarbonyl; dihydroxypropyloxycarbonyl wherein hydroxy groups are free or are protected in the form of ketals, e.g. a lower alkylidene, a benzylidene or a 5- or 6-membered cycloalkylidene derivative, advantageously being (2,2-dimethyl-1,3-dioxolan-4-yl)-methoxycarbonyl.

Carboxyl derivatized as a pharmaceutically acceptable prodrug ester represents most advantageously C_1-C_4-alkoxycarbonyl, benzyloxycarbonyl optionally substituted on phenyl by lower alkyl, lower alkoxy, halo or trifluoromethyl, 1-(C_2-C_4-alkanoyloxy)-ethoxycarbonyl, (2,2-dimethyl-1,3-dioxolan-4-yl)-methoxycarbonyl, 5-indanyloxycarbonyl, 1-(C_1-C_4-alkoxycarbonyloxy)-ethoxycarbonyl or 3-pyridylmethoxycarbonyl. Especially preferred as pharmaceutically acceptable prodrug ester is C_1-C_4-alkoxycarbonyl, e.g. methoxycarbonyl and ethoxycarbonyl.

Carboxyl derivatized as a pharmaceutically acceptable amide represents preferably carbamoyl or N-substituted carbamoyl, advantageously [lower alkylamino, arylamino, di-lower alkylamino, morpholino, N-lower alkylpiperazino, pyrrolidino, piperidino, (amino or acylamino)-lower alkylamino or aryl-lower alkylamino]-carbonyl.

The term "lower" referred to herein in connection with organic radicals or compounds respectively defines such with up to and including 7, preferably up and including 4 and advantageously one or two carbon atoms. Such may be straight chain or branched.

A lower alkyl group preferably contains 1-4 carbon atoms and represents for example ethyl, propyl, butyl or advantageously methyl.

A lower alkoxy group preferably contains 1-4 carbon atoms and represents for example methoxy, propoxy, isopropoxy or advantageously ethoxy.

Cycloalkyl represents a saturated cyclic hydrocarbon radical, preferably C_5-C_7-cycloalkyl and is, advantageously cyclopentyl or cyclohexyl.

Cycloalkyl-lower alkyl represents preferably 1- or 2-(cyclopentyl or cyclohexyl)ethyl, 1-, 2- or 3-(cyclopentyl or cyclohexyl)propyl, or 1-, 2-, 3- or 4-(cyclopentyl or cyclohexyl)-butyl.

Cycloalkoxy represents a saturated cyclic hydrocarbon radical, preferably C_5-C_7-cycloalkoxy and is, advantageously cyclopentyloxy or cyclohexyloxy.

Cycloalkyl-lower alkoxy represents preferably represents C_5-C_7-cycloalkyl-C_1-C_4-alkoxyand is, advantageously cyclopentylmethoxy or cyclohexylmethoxy.

Lower alkenyloxy represents preferably allyloxy

Lower alkylamino preferably contains 1-4 carbon atoms in lower alkyl portion and represents, for example, N-methylamino, N-ethylamino, N-propylamino and N-butylamino, and advantageously N-ethylamino.

Di-lower alkylamino preferably contains 1-4 carbon atoms in each lower alkyl portion and represents, for example, N,N-dimethylamino, N-methyl-N-ethylamino and advantageously N,N-diethylamino.

Lower alkoxycarbonyl preferably contains 1 to 4 carbon atoms in the alkoxy portion and represents, for example, methoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl or advantageously ethoxycarbonyl.

Hydroxy-lower alkyl is preferably hydroxymethyl.

Halogen (halo) preferably represents fluoro or chloro, but may also be bromo or iodo.

Lower alkanoyl is preferably acetyl, propionyl, butyryl, or pivaloyl.

Lower alkanoyloxy is preferably acetoxy, pivaloyloxy or propionyloxy.

Acylamino represents preferably lower alkanoylamino, aroylamino, or aryl-lower alkoxycarbonylamino such as benzyloxycarbonylamino.

Lower alkanoylamino is preferably acetamido or propionamido.

Aroyl is preferably benzoyl or benzoyl substituted on the benzene ring by lower alkyl, lower alkoxy, halogen or trifluoromethyl.

Acyl represents preferably lower alkanoyl, carbocyclic aryl-lower alkanoyl or carbocyclic aroyl.

Pharmaceutically acceptable salts are either pharmaceutically acceptable acid addition salts for any basic compounds of the invention or salts derived from pharmaceutically acceptable bases for any acidic compounds of the invention.

Pharmaceutically acceptable salts of any basic compounds of the invention are acid addition salts, which are preferably such of therapeutically acceptable inorganic or organic acids, such as strong mineral acids, for example hydrohalic, e.g. hydrochloric, hydrobromic, sulfuric or phosphoric acid; aliphatic or aromatic carboxylic or sulfonic acids, e.g. acetic, propionic, succinic, glycollic, lactic, malic, tartaric, gluconic, citric, maleic, fumaric, pyruvic, phenylacetic, benzoic, pamoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, 1,2-ethanedisulfonic, benzenesulfonic, p-toluenesulfonic or naphthalenesulfonic acid; or ascorbic acid.

Pharmaceutically acceptable salts of the acidic compounds of the invention, e.g. those having a carboxyl

group are salts formed with pharmaceutically acceptable bases, e.g. alkali metal salts (e.g. sodium, potassium salts), alkaline earth metal salts (e.g. magnesium, calcium salts), amine salts (e.g. ethanolamine, diethanolamine, triethanolamine, tromethamine salts).

The novel compounds of the invention have valuable pharmacological properties. They are pharmacologically potent hypolipidemic agents which reduce plasma cholesterol levels in mammals. The compounds of the invention demonstrate potent binding to thetriiodothyronine (T_3) nuclear receptor which is indicative of upregulation of LDL receptor activity and enhancement of the clearance of LDL-cholesterol from the circulation.

The compounds of the invention are thus particularly useful in mammals as hypocholesteremic agents for the treatment and prevention of occlusive cardiovascular conditions in which hypercholestermia are implicated, by reducing plasma levels of total and LDL-cholesterol. The invention furthermore relates to the use of the compounds according to the invention for the preparation of medicaments, in particular of medicaments useful for the treatment and prevention of occlusive cardiovascular conditions in which hypercholestermia are implicated, by reducing plasma levels of total and LDL-cholesterol. Also included therein is the industrial preparation of the active substances in form of a commercial package.

The above-cited properties are demonstrable in vitro and in vivo tests, using advantageously mammals, e.g. mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. Said compounds can be applied in vitro in the form of solutions, e.g. preferably aqueous solutions, and in vivo either enterally, parenteally, advantageously intravenously, e.g. as a suspension or in aqueous solution. The dosage in vitro may range between about 10^{-7} molar and 10^{-11} molar concentrations. The dosage in vivo may range depending on the route of administration, between about 0.1 and 300 micrograms/Kg, preferably between about 0.5 and 100 micrograms/Kg, advantageously between about 1 and 100 micrograms/Kg.

The in vitro binding to T_3 nuclear receptors is determined as follows:

Rat liver nuclei and plasma membrane preparations are obtained from Sprague-Dawley (CD) rats (Charles River Labs.) by differential centrifugation as described by Emmelot et al (Methods in Enzymology 31:75, Part A, 1974) with minor modifications. The nuclear fraction obtained from the 275 x g pellet is further purified as generally described by Spindler et al (J. Biol. Chem. 250:4118, 1975).

The novel test compounds are assayed for binding to the nuclei by the method of Spindler et al (J. Biol. Chem. 250:4118, 1975). The nuclei are incubated at 22°C with 0.3 nM of [^{125}I]-L-triiodothyronine (L-T_3). Parallel incubations are conducted with tubes containing, in addition to the nuclei and radioactive L-T_3, either various concentrations of the test compounds or 3 uM of nonradioactive L-T_3. The latter is used as a measure of non-specific binding. The radioactivity bound to the nuclei is determined following centrifugation of the reaction mixture at 800 x g for 7 minutes and washing of the pellet obtained. The amount of [^{125}I]-L-T_3 specifically bound is determined by subtracting the amount non-specifically bound (radioactivity contained in the nuclear pellet following incubation with excess (3 μM) non-radioactive L-T_3). The concentration of test compound which inhibits the specific binding of [^{125}I]-L-T_3 by 50 percent (IC_{50}) is determined graphically from the reciprocal plot of the specifically bound [^{125}I]-L-T_3 versus the various concentrations of the test compound.

Cholesterol lowering activity is determined in the rat as follows:

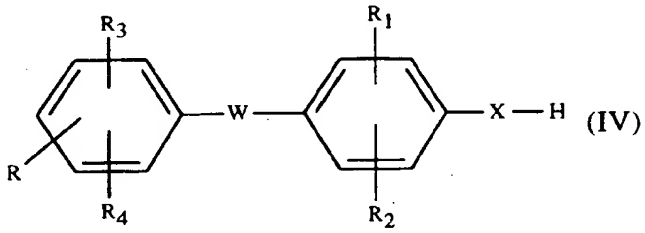
Male Sprague-Dawley rats (230-250 g) (Taconic Farms) are maintained ad libitum on water and a high cholesterol diet (1.5% cholesterol and .5% cholic acid) for two weeks prior to and during the 7-day treatment period. Groups of animals are treated orally by gavage with the vehicle alone or with test compound for 7 consecutive days. After the last dose, animals are fasted for 18 hours and blood is collected. Blood samples are centrifuged at 2500 rpm for 10 minutes to prepare plasma for total cholesterol determination as well as LDL and HDL cholesterol concentrations. HDL values are determined after LDL/VLDL precipitation (Warnick and Albers, 1978). All samples are analyzed enzymatically for cholesterol with a diagnostic reagent kit (Sigma Chemical Co., St. Louis, MO). The analysis is performed on a Bio-Mek automated work station. LDUVLDL fractions are precipitated in the following manner: 0.35 ml of plasma is aliquoted into Eppendorf tubes to which 12 μl of 2M manganese chloride, 11.2μl of sodium heparin (Porcine Intestinal, 5000 units/ml), and 8.3 μl of normal saline are added. The samples are vortexed and are placed on ice for 15 minutes, then centrifuged at 4°C for 10 minutes at 1300 rpm and the supernatant is enzymatically analyzed for cholesterol. The HDL cholesterol concentration is adjusted for dilution by multiplying the supernatant cholesterol value by 1.09. LDL/VLDL cholesterol values are obtained by subtracting HDL cholesterol from total cholesterol.

Cholesterol-lowering activity can also be evaluated in normocholesterolemic dogs fed regular chow following the procedure described above, by administration of test compound orally for 5 days; also in normolipemic cynomolgus monkeys.

Illustrative of the invention, N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamic acid demonstrates an IC_{50} of about 0.2 nM in the T_3 nuclear receptor binding assay. Furthermore, said compound significantly lowers serum cholesterol at a daily dose of about 20 micrograms (μg)/Kg p.o. in the rat and about 30 μg/Kg p.o. in the dog. As a further illustration, ethyl N-[4-[3'-[(4-fluorophenyl)hydroxymethyl]-4'-hydroxy-

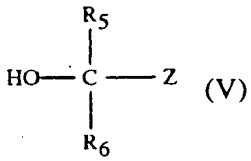
phenoxy]-3,5-dimethylphenyl]oxamate (IC_{50}=0.1 nM) significantly lowers serum cholesterol at a daily dose of about 5 μg/Kg p.o. in the rat, of about 10 μg/Kg p.o. in the dog and of about 1 μg/Kg p.o. in the monkey.

The compounds of the invention can be prepared by condensing a compound of the formula



(IV)

wherein R, R_1-R_4, W and X have meaning as defined hereinabove, advantageously with a reactive functional derivative of a compound of the formula V



(V)

wherein R_5, R_6 and Z have meaning as defined hereinabove, in protected form as required; and in above said process, if temporarily protecting any interfering reactive group(s), removing said protecting group(s), and then isolating the resulting compound of the invention; and, if desired, converting any resulting compound of the invention into another compound of the invention; and/or, if desired, converting a free carboxylic function into a pharmaceutically acceptable ester or amide derivative, or converting a resulting ester or amide into the free acid or into another ester or amide derivative; and/or, if desired, converting a resulting free compound into a salt or a resulting salt into the free compound or into another salt, and/or, if desired, separating a mixture of isomers or racemates obtained into the single isomers or racemates, and/or, if desired, resolving a racemate obtained into the optical antipodes.

In starting compounds and intermediates which are converted to the compounds of the invention in a manner described herein, functional groups present, such as carboxyl, amino and hydroxy groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected carboxyl, amino and hydroxy groups are those that can be converted under mild conditions into free carboxyl, amino and hydroxy groups without other undesired side reactions taking place.

The purpose of introducing protecting groups is to protect the functional groups from undesired reactions with reaction components and under the conditions used for carrying out a desired chemical transformation. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional group to be protected (hydroxy, carboxyl group, amino group etc.), the structure and stability of the molecule of which the substituent is a part, and the reaction conditions.

Well-known protecting groups that meet these conditions and their introduction and removal are described, for example, in J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, New York 1973, T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1984, and also in "The Peptides", Vol. I, Schroeder and Luebke, Academic Press, London, New York, 1965.

Reactive functional derivatives of compounds of formula V (oxalic acid derivatives) are preferably halides, mixed anhydrides such as the pivaloyl or alkoxycarbonyl anhydride, and esters such as lower alkyl esters.

The condensation (acylation), according to the above process, of a compound of formula V with a reactive functional derivative of a compound of formula V is carried out according to methodology well-known in the art, by reacting such without solvent at elevated temperature, or in an inert solvent, such as dimethylformamide or methylene chloride, advantageously in the presence of a base, such as potassium carbonate, triethylamine, diisopropylethylamine, pyridine and the like at room or elevated temperature.

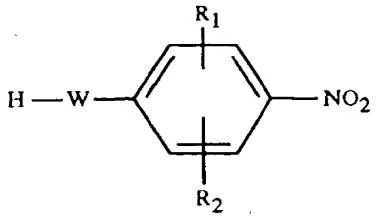
For example, relating to the preparation of compounds wherein R_5 and R_6 together represent oxo, a compound of formula IV in which XH represents e.g. NH2, is condensed with an ester or amide derivative of oxalic acid, such as diethyl oxalate (the reactive derivative of a compound of formula V), using diethyl oxalate as both reagent and solvent, at elevated temperature. Alternatively, a hemiester-hemihalide of oxalic acid, e.g.

ethyl oxalyl chloride can be used as the reactive derivative of a compound of formula V, and the condensation is carried out e.g. in an inert solvent, such as methylene chloride, and in the presence of a base, such as potassium carbonate or triethylamine. If a hemiester-hemiamide of oxalic acid is used, the corresponding amide is obtained.

The starting materials of formula V are either known or can be prepared according to methods known in the art.

The starting materials of formula IV wherein XH represents NH_2 can e.g. be prepared by

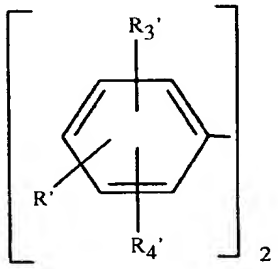
(a) condensing a 4-nitrophenol (or corresponding thiophenol) appropriately substituted by R_1 and R_2 of the formula VI



(VI)

wherein R_1, R_2 and W have meaning as defined hereinabove,

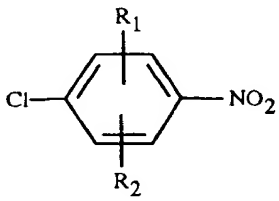
with a bis-aryl iodonium tetrafluoroborate appropriately substituted by R', R_3' and R_4' of the formula VII



$I^+ \ BF_4^-$ (VII)

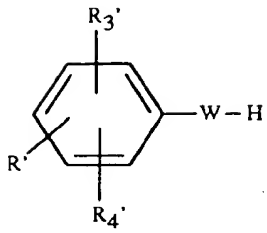
wherein R', R_3' and R_4' represent R, R_3 and R_4 as defined hereinabove, or R', R_3' and R_4' are groups convertible to R, R_3 and R_4, respectively, in the presence of e.g. copper, a base such as triethylamine and an inert solvent such as methylene chloride; or

(b) condensing a 4-chloronitrobenzene appropriately substituted by R_1 and R_2 of the formula



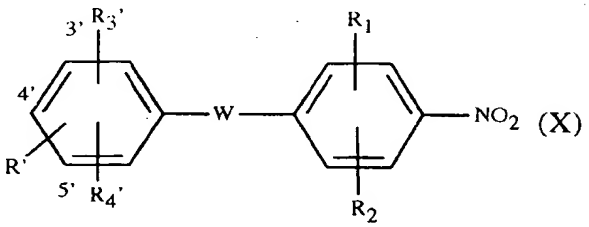
(VIII)

with a phenol (or thiophenol) appropriately substituted by R', R_3' and R_4' of the formula



(IX)

wherein R', R_3', R_4' and W have meaning as defined hereinabove in the presence of a base, such as potassium carbonate in a polar inert solvent such as dimethylsulfoxide or N-methylpyrrolidone; and
(c) reducing a resulting compound of the formula X



(X)

wherein R', R_1, R_2, R_3', R_4' and W have meaning as defined hereinabove, e.g. by catalytic hydrogenation in the presence of e.g. Raney nickel or palladium on charcoal as catalyst, in a polar solvent, such as glacial acetic acid or ethanol, to obtain an amine intermediate of formula V or an amine intermediate convertible to an amine intermediate of formula IV.

The bis-aryl iodonium tetrafluoroborates of formula VII, e.g. wherein R' represents 4'-alkoxy or 4'-benzyloxy (which may be further substituted by e.g. lower alkyl) can be prepared e.g. by condensation of the corresponding optionally substituted anisole or benzyloxy benzene with di-(trifluoroacetyl)-iodonium tetrafluoroborate (prepared from iodine, nitric acid, acetic anhydride, trifluoroacetic acid and sodium tetrafluoroborate) according to methods known in the art and illustrated herein.

A 4-chloronitrobenzene of formula VIII can be prepared from the corresponding 4-nitrophenol of formula VI by first converting such to e.g. the trifluoromethylsulfonyl ester, and treating the latter with lithium chloride in an inert solvent such as N-methylpyrrolidone or dimethylformamide. The 4-nitrophenol can in turn be prepared by nitration of the phenol under conditions well-known in the art, e.g. with nitric acid in acetic acid or with nitronium tetrafluoroborate.

The appropriately substituted phenols and thiophenols of formula IX are known in the art or are prepared as illustrated herein.

For example, a compound of formula IX can be prepared by Fries type rearrangement of an acetic acid ester of the appropriately substituted phenol with e.g. aluminum chloride to obtain the appropriately substituted hydroxyacetophenone, which is protected as an ether, and subsequently oxidized under Baeyer-Villiger conditions, e.g. with peracetic acid to the acetic acid ester of the substituted phenol, which is then hydrolyzed to the phenol of formula IX.

Intermediates of formula X wherein R' represents e.g. 4'-lower alkoxy or 4'-benzyloxy, and R_3' and R_4' are hydrogen, can be converted to intermediates of formula X wherein R_3' is the radical 3'-R_8-CO- and R_8 has meaning as defined hereinabove, by treating a said intermediate of formula X under Friedel-Crafts acylation conditions with a reactive derivative of a carboxylic acid R_8-COOH, such as the acid chloride or anhydride, in the presence of a Lewis acid.

For example, acylation of a compound of formula X wherein R' is 4'-alkoxy or 4'-benzyloxy, and R_3' and R_4' represent hydrogen, with an aroyl chloride, such as optionally substituted benzoyl chloride in the presence of titanium chloride in methylene chloride yields the corresponding compound of formula X wherein R' is 4'-alkoxy or 4'-benzyloxy, R_3' is 3'-aroyl, and R_4' is hydrogen.

Subsequent conversion to a compound of formula X wherein R' is 4'-hydroxy is achieved according to methods well known in the art, e.g. with acid such as hydrochloric acid or a boron trihalide, such as boron trichloride or boron tribromide when R' is in particular 4'-methoxy.

Intermediates, e.g. of formula X, wherein R_3' is aroyl can be reduced to corresponding compounds wherein

R_3' is arylmethyl by reduction with e.g. triethylsilane and trifluoroacetic acid in methylene chloride.

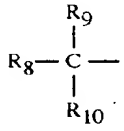
Intermediates, e.g. of formula X, wherein R_3' is e.g. aroyl can be reduced to the corresponding compounds wherein R_3' is aryl-hydroxymethyl using e.g. an alkali metal borohydride such as sodium or lithium borohydride in a polar solvent such as methanol or acetic acid. Said ketone intermediate, of formula XII, wherein R_3' represents e.g. aroyl can also be reduced by catalytic hydrogenation to obtain the corresponding amine intermediates of formula V wherein XH represents NH_2 and R_3 represents aryl-hydroxymethyl.

The intermediates of formula IV wherein XH represents NH_2 may be converted to intermediates wherein XH represents NHR_7 according to methods well-known in the art for conversion of a primary to a secondary amine, such as by reductive alkylation. In the case where R_7 represents methyl, the transformation can be accomplished e.g. by treatment with ethyl chloroformate followed by reduction with lithium aluminum hydride.

The compounds of the invention can be converted into each other according to conventional methods. Thus, for example, resulting amides or esters may be hydrolyzed with aqueous alkalies, such as alkali metal carbonates or hydroxides. Resulting free acids may be esterified with e.g. said unsubstituted or substituted alkanols or reactive esterified derivatives thereof such as alkyl halides, or diazoalkanes. Free acids are also converted into said metal, ammonium or acid addition salts in conventional manner.

Thus, any resulting free acid can be converted into a corresponding metal, ammonium or acid addition salt respectively, by reacting it with an equivalent amount of the corresponding base, or ion exchange preparation, e.g. said free acids with alkali or ammonium hydroxides or carbonates. Any resulting salt may also be converted into the free compound, by liberating the latter with stronger acids. In view of the close relationship between the free compounds and the salts thereof, whenever a compound of the invention, or intermediate, is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

Compounds according to the invention in which R_3 represents a group (a)



(a)

in which R_9 and R_{10} together represent oxo, may be converted into compounds according to the invention in which R_3 represents a group (a) in which R_9 is hydrogen and R_{10} is hydroxy, for example by reduction, for example by treatment with a suitable, optionally complex, hydride, such as a hydride formed from an element of Groups 1 and 3 of the Periodic Table of Elements, for example borohydride or sodium cyanoborohydride. Compounds according to the invention in which R_3 represents a group (a) in which R_9 is hydrogen and R_{10} is hydroxy, may be reduced to compounds according to the invention in which R_3 represents a group (a) in which R_9 and R_{10} represent hydrogen, for example with hydrogen using a hydrogenation catalyst.

The compounds, including their salts, may also be obtained in the form of their hydrates, or include other solvents used for the crystallization. Furthermore, the functional derivatives of the free acids of formula I, e.g. wherein carboxy is esterified may be prepared by condensing a free acid of formula I with an esterifying agent of the formula XI

$$R_9\text{-}Y \qquad (XI)$$

wherein Y represents hydroxy or a reactive esterified hydroxyl group; and R_9 represents an esterifying radical as defined herein for the esters (esterified carboxy).

A reactive esterified hydroxyl group, such as Y in a compound of the formula XI, is a hydroxyl group esterified by a strong inorganic or organic acid. Corresponding Y groups are in particular halo, for example chloro, bromo or preferably iodo, also sulfonyloxy groups, such as lower alkyl- or arylsulfonyloxy groups, for example (methane-, ethane-, benzene- or toluene-) sulfonyloxy groups, also the trifluoromethylsulfonyloxy group.

The esterification of the carboxyl group, optionally in salt form, with a compound of formula XI wherein Y represents a reactive esterified hydroxyl group, is performed in a manner known per se, in the presence of for example an organic base, such as an organic amine, for example a tertiary amine, such as tri-lower alkylamine, for example trimethylamine, triethylamine or ethyl-di-isopropylamine, an N,N-di-lower-alkyl-aniline, for example N,N-di-methylaniline, a cyclic tertiary amine, such as an N-lower-alkylated morpholine, for example N-methyl-morpholine, a base of the pyridine type, for example pyridine, an inorganic base, for example hydroxides, carbonates, or hydrogen carbonates of alkali metals or alkaline-earth metals, for example sodium, potassium or calcium hydroxide, carbonate or hydrogen carbonate, or a quaternary ammonium base, such as a tetraalkylammonium hydroxide, carbonate or hydrogen carbonate, for example in which alkyl is e.g. methyl, ethyl, propyl, isopropyl, butyl, or the like, or an alkali metal salt of bis-trialkylsilylamide (e.g. trimethyl) optionally in the

presence of a crown ether such as 18-crown-6 in a suitable inert solvent or solvent mixture, e.g. acetonitrile, toluene, and the like.

Esterification of a compound with a free carboxyl group using in excess an alcohol of formula XI (wherein Y represents hydroxy) is carried out in a manner known per se, e.g. in the presence of an acid catalyst e.g. sulfuric acid or boron trifluoride etherate, preferably at an elevated temperature, advantageously ranging from about 40°C to 100°C. Alternatively, the esterification of a compound with a free carboxyl group can be carried out with at least an equimolar amount of the alcohol in the presence of a condensing agent such as dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide in a polar solvent such as methylene chloride, in the presence of a base if required, e.g. such as 4-(dimethylamino)pyridine.

Similarly, the free carboxylic acids can be converted to amides using methods well known in the art, e.g. in the presence of a condensing agent such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ).

Conversely, carboxylic acid esters can be converted to compounds of the invention with a free carboxy group using the methods and conditions generally known in the art and illustrated herein. Depending on type of ester involved, useful reagents include aqueous acids or bases. Any benzyl esters can be selectively hydrogenolyzed with e.g. hydrogen in the presence of a catalyst such as palladium on charcoal.

Compounds wherein R represents esterified hydroxy or etherified hydroxy can be converted to the compounds wherein R represents hydroxy using methods well-known in the art.

For example, compounds wherein R represents e.g. methoxy can be treated with boron tribromide or boron trichloride in e.g. dichloromethane to obtain compounds wherein R is hydroxy. Also, if R represents benzyloxy, such can be debenzylated by hydrogenolysis with hydrogen in the presence of e.g. palladium catalyst. In the case of esterified hydroxy such can be deesterified with e.g. aqueous acid or base, such as lithium or sodium hydroxide.

In the case mixtures of stereoisomers or optical isomers are obtained, these can be separated into the single isomers by methods in themselves known, e.g. on the basis of the physicochemical differences of the components, for example by fractional crystallization. Racemic products or intermediates may be resolved into the optical antipodes by known methods, for example by separation of diasteromeric salts thereof, by recrystallization [e.g. for basic compounds by the fractional crystallization of d- or 1-(tartrate, mandelate or camphorsulfonate) salts, or for acidic compounds by franctional crystallization of d- or 1-(alpha-methylbenzylamine, cinchonidine, cinchonine, quinine, quinidine, ephedrine, dehydroabietylamine, brucine or strychnine)-salts], from an optically active solvent, chromatography on chiral adsorbents, with the aid of suitable microorganisms, by cleavage with specific immobilized enzymes, via the formation of inclusion compounds, for example using chiral crown ethers, only one enantiomer being complexed, or by conversion into diastereomeric salts, for example by reaction of a basic final substance racemate with an optically active acid, such as a carboxylic acid, for example tartaric or malic acid, or sulfonic acid, for example camphorsulfonic acid, and separation of the diastereomer mixture obtained in this manner, for example on the basis of its differing solubilities, into the diastereomers from which the desired enantiomer can be liberated by the action of suitable agents.

The above-mentioned transformations are carried out according to standard methods for the reactions involved, in the presence or absence of diluents, preferably such as are inert to the reagents and are solvents thereof, of catalysts, alkaline or acidic condensing or said other agents respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures, preferably near the boiling point of the solvents used, at atmospheric or superatmospheric pressure.

The present invention relates also to novel starting materials that have been developed specifically for the manufacture of the compounds according to the invention, especially the selection of starting materials resulting in the final compounds referred to at the beginning as being preferred, wherein the variables have the meanings as indicated, to processes for the manufacture thereof, and to the use as intermediates.

The invention further includes any variant of said processes, in which an intermediate product obtainable at any stage of the process is used as a starting material and any remaining steps are carried out, or the process is discontinued at any stage thereof, or in which the starting materials are formed under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes. Mainly those starting materials should be used in said reactions, that lead to the formation of those compounds indicated above as being preferred.

The invention relates especially to the processes described in the Examples.

The present invention additionally relates to the use in mammals for the treatment of hypercholesterolemia of the compounds of the invention or pharmaceutical compositions thereof, e.g. as cholesterol lowering agents, e.g. for lowering LDL-cholesterol, by administration to a mammal in need thereof of a therapeutically effective amount of a said compound.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal and parenteral administration to mammals, including man, for the treatment of hyper-

cholesterolemia, comprising an effective amount of a pharmacologically active compound of the invention, alone or in combination with one or more pharmaceutically acceptable carriers.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application.

Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salts and/or polyethyleneglycol; for tablets also c) binders, e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired, d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, the compositions may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75%, preferably about 1 to 50%, of the active ingredient.

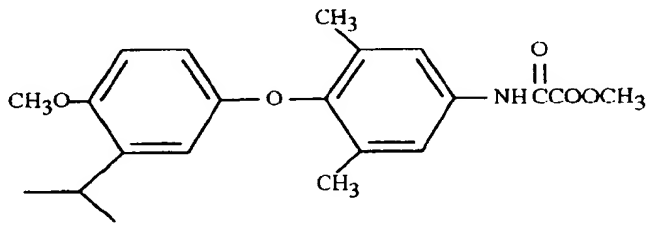
Suitable formulations for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound, optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

A unit dosage for a mammal of about 50 to 70 kg may contain between about 0.01 mg and 10 mg of the active ingredient. The dosage of active compound is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, on the form of administration, and on the compound involved.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 and 100 mm Hg. Reduced pressures are expressed as mmHg or Torr. Hydrogenation pressures are indicated as atmospheres or psi (pounds/square inch). Other abbreviations are those standard in the art.

Example 1

To 3,5-dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)-aniline (5.8 g) is added 37.5 g of dimethyl oxalate and this mixture is stirred at 120° for 4 hours Excess dimethyl oxalate is removed under high vacuum in a hot water bath and the residue is chromatographed on silica gel using 95:5 to 90:10 toluene:ethyl acetate as eluent to yield crude product which is crystallized from toluene to give methyl N-[3,5-dimethyl-4-(4'-methoxy-3'-isopropylphenoxy)-phenyl] oxamate. NMR ($CDCl_3$):δ1.1 (6H,d), 2.1 (6H,s), 3.2 (1H,m), 3.7 (3H,s), 4.0 (3H,s), 6.3 (1H,d of d), 6.6 (1H,d), 6.7 (1H,d), 7.3 (2H,s) 8.7 (1H,s). The structural formula is



The starting material is prepared as follows:

2-Isopropylphenol (300 g), 262 ml of dimethyl sulfate, and 1500 g of potassium carbonate in 1 liter of acetone are stirred mechanically and refluxed for 6 1/2 hours. The mixture is filtered and the filter cake washed with acetone. The combined filtrate is stripped, the residue is redissolved in ether, then extracted with 2N sodium hydroxide (twice) and brine (once). The ether is dried, filtered, and stripped to leave an oil which is distilled under high vacuum to afford 2-isopropylanisole, b.p. 39°.

Concentrated nitric acid (>90%, 12.4 ml) is added dropwise to 31.4 ml acetic anhydride chilled in dry ice/car-

bon tetrachloride. Iodine (11.26 g) is added in one portion followed by 20.5 ml of trifluoroacetic acid dropwise. The mixture is stirred at room temperature until all the iodine dissolves and nitrogen oxides are then purged with nitrogen gas. The solution is then stripped under high vacuum at <40° to give a solid which is redissolved in 126 ml acetic anhydride and recooled in dry ice/carbon tetrachloride. 2-Isopropylanisole (40 g), 151 ml acetic anhydride, and 22.6 ml trifluoroacetic acid are added dropwise and the solution obtained is allowed to stand in a refrigerator overnight. This solution is stripped under high vacuum at <40°, taken up in 150 ml methanol, and treated with 150 ml of 10% (w/v) sodium bisulfite and 1 liter of 2F sodium tetrafluoroborate. When the precipitate has aggregated the supernatant is decanted and the residue triturated with hexane to give crystals which are filtered, washed with hexane, and dried at room temperature in vacuo to afford bis-(3-isopropyl-4-methoxyphenyl) iodonium tetrafluoroborate.

Bis (3-Isopropyl-4-methoxyphenyl) iodonium tetrafluoroborate (116.51 g) and 19.26 g of copper bronze are stirred in 300 ml dichloromethane cooled in an ice water bath. A mixture of 25.36 g of 2,6-dimethyl-4-nitrophenol and 16.88 g of triethylamine is added dropwise. The mixture is stirred in the dark for five days, then filtered through Celite to remove copper. The filtrate is stripped and the residue chromatographed on silica gel with 97:3 hexane:ethyl acetate as eluent, affording 3,5-dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)-nitrobenzene NMR($CDCl_3$): δ 1.1 (6H,d), 2.2 (6H,s), 3.3 (1H,m), 3.7 (3H,s), 6.3 (1H,d of d), 6.6 (1H,d), 6.7 (1H,d), 8.0 (2H,s).

3,5-Dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)-nitrobenzene can also be prepared as follows:

2,6-Dimethyl-4-nitrophenol (5.00 g) and 6.05 ml pyridine in 50 ml dichloromethane are cooled in an ice/salt bath and 6.04 ml of trifluoromethanesulfonic anhydride is added over 30 minutes. After stirring cold for an hour the mixture is quenched with 25 ml water, the layers separated, and the organic phase successively washed with 2N hydrochloric acid (twice), water (twice), 2N sodium hydroxide, and water (twice). Solvent is dried, filtered, and stripped to afford 2,6-dimethyl-4-nitrophenyl trifluoromethanesulfonate. NMR ($CDCl_3$): δ 2.5 (6H, s), 8.0 (2H, s).

2,6-Dimethyl-4-nitrophenyl trifluoromethanesulfonate (8.54 g) and 3.63 g of lithium chloride in 40 ml DMF are heated at 150° for four hours. Solvent is then evaporated, the residue stirred with water and ethyl acetate, filtered, and the filtrate separated. The ethyl acetate is then dried, filtered and stripped, and the residue chromatographed on silica gel with 98:2 hexane:ethyl acetate, affording 4-chloro-3,5-dimethyl-nitrobenzene. NMR ($CDCl_3$): δ 2.5 (6H,s), 7.9 (2H,s).

4-Chloro-3,5-dimethylnitrobenzene (2.12 g), 1.9 g of 3-isopropyl-4-methoxyphenol, and 1.74 g of potassium carbonate are heated 18 hrs at 125° in 25 ml dimethylsulfoxide. The mixture is poured into ethyl acetate and extracted once with water and five times with brine. The ethyl acetate is dried, filtered, and stripped to yield an oil which is chromatographed on silica gel with 97:3 hexane:ethyl acetate to afford 3,5-dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)-nitrobenzene. NMR ($CDCl_3$): δ 1.1 (6H,d), 2.2 (6H,s), 3.3 (1H,m), 3.7 (3H,s) 6.3 (1H,d of d), 6.6 (1H,d), 6.7 (1H,d), 8.0 (2H,s).

3,5-Dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)-nitrobenzene (6.0 g) and 600 mg of 10% platinum on carbon in 200 ml ethanol are hydrogenated on a Parr shaker. Catalyst is removed by filtration through Celite and the filtrate is stripped to afford 3,5-dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)-aniline.

Example 2

(a) To 10 g of methyl N-[3,5-dimethyl-4-(4'-methoxy-3'-isopropylphenoxy)-phenyl]-oxamate in 150 ml. dichloromethane cooled in dry ice/acetone is added 54 ml of 1M boron tribromide in dichloromethane. The bath is then removed and after stirring overnight the mixture is poured into ice. The layers are separated and the aqueous phase is extracted with ethyl acetate twice. The combined organic phases are dried, filtered, and stripped to give crude acid. Reesterification is effected by dissolving such in 100 ml dimethylformamide, cooling in an ice bath, and treating with 9.15 g. cesium carbonate and 2.66 ml dimethyl sulfate. After stirring at ambient overnight, the mixture is decanted into ethyl acetate and washed six times with brine. The organic phase is dried, filtered, and stripped to give an oil which is chromatographed on silica gel with 90:10 to 75:25 hexane:ethyl acetate to give methyl N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]-oxamate.

(b) 1.0N Sodium hydroxide (51 ml) is added to 8.70 g of methyl N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamate in 125 ml methanol, the mixture is refluxed 30 minutes, then cooled to room temperature. Solvent is evaporated, the residue dissolved in water, and extracted with ether twice. The aqueous layer is chilled in ice and acidified with concentrated hydrochloric acid. The resulting solid is collected, dissolved in ethyl acetate and the solution dried, filtered, and stripped. The residue is crystallized from toluene to give N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamic acid, m.p. 183-185°.

Example 3

3,5-Dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)-aniline (10.8 g) is fused at 120° for 4 hours with 50 g. of ethyl oxamate. The cooled mixture is twice triturated with hot water, then stirred with ethyl acetate, filtered to remove insolubles, and the ethyl acetate dried, filtered, and stripped to afford an oily solid. Purification is effected by chromatography on silica gel with 95:5 to 80:20 toluene:ethyl acetate as eluent to give N-[3,5-dimethyl-4-(4'-methoxy-3'-isopropylphenoxy)-phenyl]-oxamide. NMR (D_3COD): δ 1.1 (6H,d), 2.1 (6H,S), 3.2 (1H,m), 3.8 (3H,s), 6.4 (1H,d of d), 6.7 (1H,d), 6.8 (1H,d), 7.5 (2H,s).

The starting material is prepared as follows:

3,5-Dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)nitrobenzene (480 mg) and 50 mg of 10% platinum on carbon in 100 ml ethanol are reduced on a Parr shaker. Catalyst is removed by filtration through Celite and the filtrate stripped. The residue is taken up in ether and acidified with gaseous hydrogen chloride. The ether solution is chilled, filtered to remove insolubles, and stripped to afford 3,5-dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)-aniline hydrochloride, m.p. 95-100°.

Example 4

N-[3,5-Dimethyl-4-(4'-methoxy-3'-isopropylphenoxy)-phenyl]-oxamide (2.5 g) is suspended in 150 ml dichloromethane. 1M Boron tribromide in dichloromethane (30 ml) is added with dry ice/acetone cooling and the solution then allowed to stir at ambient for 18 hours. Decantation into ice followed by separation of layers and reextraction with dichloromethane gives a solution which is dried, filtered, and stripped, yielding crude product. Crystallization from toluene affords N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]-oxamide, m.p. 112-42°.

Example 5

3,5-Dichloro-4-(3'-isopropyl-4'-methoxyphenoxy)-nitrobenzene (2.0 g) and 200 mg. of 10% platinum on carbon in 100 ml. of ethanol are hydrogenated on a Parr shaker. Catalyst is then removed by filtration through Celite and the filtrate is stripped to afford 3,5-dichloro-4-(3'-isopropyl-4'-methoxyphenoxy)-aniline. To this is added 30 g of dimethyl oxalate and this is stirred at 120° for 4 hours. Excess oxalate is removed under high vacuum from a hot water bath and the residue is chromatographed on silica gel with 9:1 toluene:ethyl acetate affording methyl N-[3,5-dichloro-4-(4'-methoxy-3'-isopropylphenoxy)-phenyl]oxamate; NMR($CDCl_3$): δ 1.2 (6H,d) 3.3 (1H,m), 3.8 (3H,s), 4.0 (3H,s), 6.5 (1H,d of d), 6.7 (1H,d), 6.8 (1H,d), 7.7 (2H,s).

The starting material is prepared as follows:

To 31 g of 2,6-dichlorophenol in 120 ml acetic acid cooled in an ice bath is added over 5 minutes 50 ml of 70% nitric acid. After stirring an hour at room temperature, the mixture is purged with nitrogen, then poured into water, filtered; the product is washed with water and dried in vacuo to give 2,6-dichloro-4-nitrophenol. NMR (CD_3OD): δ 8.2(s).

Bis-(3-Isopropyl-4-methoxyphenyl)iodonium tetrafluoroborate (38.3 g) and 6.33 g of copper bronze are stirred in 150 ml dichloromethane and cooled in an ice water bath. A solution of 10.37 g of 2,6-dichloro-4-nitrophenol and 5.5 g of triethylamine is added dropwise. The mixture is stirred in the dark at room temperature for three days, then filtered through Celite to remove copper. The filtrate is stripped and the residue chromatographed on silica gel with 97:3 to 95:5 hexane-ethylacetate as eluent to give 3,5-dichloro-4-(3'-isopropyl-4'-methoxyphenoxy)-nitrobenzene, m.p. 75-7°.

Example 6

To 16.21 g of methyl N-[3,5-dichloro-4-(4'-methoxy-3'-isopropylphenoxy)-phenyl]oxamate in 400 ml dichloromethane cooled in dry ice/acetone is added 79 ml of 1M boron tribromide in dichloromethane. The bath is removed and after stirring overnight the mixture is poured into ice. After melting of the ice, the layers are separated and the aqueous phase is twice extracted with ethyl acetate. The combined organic phases are dried, filtered, and stripped to give crude acid. Reesterification is effected by dissolving in 150 ml dimethylformamide, cooling in an ice bath, and treating with 12.81 g. of cesium carbonate and 3.8 ml. of dimethyl sulfate. After stirring at ambient overnight, the mixture is decanted into ethyl acetate and extracted six times with brine. The organic phase is dried, filtered, and stripped, and the residue chromatographed on silica gel with 90:10 to 50:50 toluene-ethyl acetate to give methyl N-[3,5-dichloro-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamate. This is taken up in 100 ml methanol, treated with 55 ml of 1N sodium hydroxide solution, refluxed 30 minutes, and cooled to room temperature. Solvent is stripped, the residue taken up in water, and extracted twice

with ether. The aqueous phase is cooled in an ice bath, acidified with concentrated hydrochloric acid, and extracted with ethyl acetate; the extract is then dried, filtered, and stripped to give crude product. Crystallization from toluene affords N-[3,5-dichloro-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]-oxamic acid, m.p. 180-2°dec.

Example 7

Similarly prepared to procedures described in the previous examples are:
(a) N-[3,5-dibromo-4-(3'-isopropyl-4'-hydroxyphenoxy)-phenyl]-oxamic acid, m.p. 192-194° dec.
(b) N-[3,5-diiodo-4-(3'-isopropyl-4'-hydroxyphenoxy)-phenyl]-oxamic acid, m.p. 201-204° dec.
(c) N-[4-(3'-isopropyl-4'-hydroxyphenoxy)-phenyl]-oxamic acid, m.p. 105-110° dec.
(d) N-[3,5-dibromo-4-(3'-isopropyl-4'-hydroxy-phenoxy)-phenyl]-oxamide, m.p. 86-90°.
(e) N-[3,5-diisopropyl-4-(3'-isopropyl-4'-hydroxyphenoxy)-phenyl]-oxamic acid, m.p. 72-90°.
(f) N-[3,5-dimethyl-4-(4'-hydroxyphenoxy)-phenyl]-oxamic acid, m.p. 199-200°.
(g) N-[3,5-dimethyl-4-(3'-ethyl-4'-hydroxyphenoxy)-phenyl]-oxamic acid, m.p. 177-178° dec.
(h) N-[3-methyl-4-(3'-isopropyl-4'-hydroxyphenoxy)-phenyl]-oxamic acid, m.p. 133-137°.
(i) N-[3,5-dimethyl-4-(3'-isopropyl-4'-hydroxyphenoxy)-phenyl]-N-methyloxamic acid, m.p. 140-156° dec.
The starting material is prepared as follows:

3,5-Dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)-aniline (2.57g) and 1.73 ml of diisopropylethylamine in 30 ml of dry THF cooled in an ice bath are treated with .95 ml of ethyl chloroformate. After stirring at room temperature for 18 hours the mixture is stripped, then dissolved in ethyl acetate and extracted with water. The organic phase is dried, filtered, and stripped to give a crude oil. Chromatography on silica gel with 9:1 hexane:ethyl acetate gives ethyl N-[3,5-dimethyl-4-(4'-methoxy-3'-isopropylphenoxy)-phenyl]carbamate. NMR ($CDCl_3$): δ 1.0 (6H,d), 1.2 (3H,t), 2.0 (6H,s), 3.3 (1H,m), 3.7 (3H,s), 4.2 (2H,q), 6.3 (1H,d of d), 6.6 (1H,d), 6.7 (1H,d), 7.1 (2H,s).

To 650 mg of lithium aluminum hydride suspended in 100 ml dry tetrahydrofuran cooled in an ice bath is added dropwise a solution of 3.06 g of ethyl N-[3,5-dimethyl-4-(4'-methoxy-3'-isopropylphenoxy)-phenyl]carbamate in 20 ml. dry tetrahydrofuran. The mixture is refluxed three hours, then cooled in an ice bath and heated with 0.65 ml water, 0.65 ml 15% sodium hydroxide, and 1.95 ml water. The precipitate is filtered off, washed with tetrahydrofuran, and the filtrate concentrated. Chromatography on silica gel with toluene to 95:5 toluene:ethyl acetate affords N-methyl-3,5-dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)-aniline. NMR ($CDCl_3$): δ 1.2 (6H,d), 2.1 (6H,s), 2.8 (3H,s), 3.3 (1H,m), 3.8 (3H,s), 6.4 (3H,m), 6.7 (1H,d), 6.8 (1H,d).
(j) N-[3,5-diiodo-4-(4'-hydroxyphenoxy)-phenyl]-oxamic acid;
(k) N-[3,5-dichloro-4-(4'-hydroxyphenoxy)-phenyl]-oxamic acid;
(l) N-[3,5-difluoro-4-(3'-isopropyl-4'-hydroxyphenoxy)-phenyl]-oxamic acid; m.p. 160-162°.
(m) N-[3-methyl-4-(3'-isopropyl-4'-hydroxyphenoxy)-phenyl]-oxamic acid, m.p. 133-137°.
The intermediate, 2-methyl-4-nitrophenol, is prepared as follows:

2-Methylanisole (20 g) in 500 ml dichloromethane chilled in an ice bath is treated with 27.2 g of nitronium tetrafluoroborate and stirred two days. The mixture is poured into water, the layers are separated, and the aqueous phase is washed with dichloromethane. The combined organic layers are dried, filtered, stripped, and chromatographed on silica gel with 9:1 to 8:2 hexane:ethyl acetate to give 2-methyl-4-nitroanisole. NMR ($CDCl_3$): δ 2.3 (3H,s), 3.9 (3H,s), 6.9 (1H,d), 8.0 (1H,d), 8.1 (1H,d of d).

2-Methyl-4-nitroanisole (4.0 g) in 50 ml 1:1 hydrobromic acid:acetic acid is heated 12 hours at 120°. Solvent is stripped, the residue taken up in water and ethyl acetate, the mixture is filtered to remove insolubles, and the layers are separated. The organic phase is dried, filtered, and stripped to afford 2-methyl-4-nitrophenol. NMR ($CDCl_3$): δ 2.3 (3H,s), 6.8 (1H,d), 7.9 (1H,d of d), 8.0 (1H,d).

Example 8

N-[3,5-Dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamic acid (500 mg) and 290 mg of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline are dissolved in 20 ml. of dimethylformamide. The solution is saturated with methylamine gas, capped, and stirred at ambient for three days. Solvent is removed under high vacuum and the residue chromatographed on silica gel with 95:5 toluene:ethyl acetate to 75:25 ethyl acetate:-ethanol to afford N-[3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]-N'-methyloxamide, m.p. 140-5°.

Example 9

Methyl N-[3,5-dimethyl-4-(4'-methoxy-3'-isopropylphenoxy)phenyl]oxamate (2.02 g) in 50 ml methanol is treated with 6.0 ml of 1.0 N sodium hydroxide, refluxed 1/2 hour, and cooled to ambient. Solvent is evaporated,

the residue dissolved in water, extracted with ether, and the aqueous phase neutralized with 6 ml of 1.0 N hydrochloric acid. The resulting precipitate is washed with water, taken up in ethyl acetate and ethanol and the solution dried, filtered, and stripped to leave crude product which is crystallized from toluene to afford N-[3,5-dimethyl-4-(4'-methoxy-3-isopropylphenoxy)-phenyl]-oxamic acid, m.p. 179-83° (dec.).

Example 10

(a) N-[3,5-Dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamic acid (8.48 g), 8.04 g of cesium carbonate, and 2.4 ml of dimethyl sulfate are stirred overnight in 50 ml dimethylformamide. The mixture is poured into ethyl acetate and extracted once with water and five times with brine. The organic layer is dried, filtered, and stripped to afford an oil which is chromatographed on silica gel with from 90:10 to 50:50 toluene:-ethyl acetate to give purified material which is then crystallized from toluene to afford methyl N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamate, m.p. 190-3°.

(b) N-[3,5-Dichloro-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamic acid (9.59 g), 8.13 g of cesium carbonate, and 2.4 ml of dimethyl sulfate are stirred overnight in 50 ml dimethylformamide. The mixture is poured into ethyl acetate and extracted once with water and five times with brine. The organic layer is dried, filtered, and stripped and the residue chromatographed on silica gel with from 90:10 to 50:50 toluene:ethyl acetate to yield desired product which is crystallized from toluene to produce methyl N-[3,5-dichloro-4-(4' -hydroxy-3'-isopropylphenoxy)-phenyl]oxamate, m.p. 181-5°.

Example 11

N-[3,5-Dichloro-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamic acid (3.0 g), 2.55 g of cesium carbanate and 0.93 ml of benzyl bromide are stirred in 20 ml dimethylformamide overnight. The mixture is poured into ethyl acetate and extracted with water once and brine five times. The organic layer is dried, filtered, and stripped and the residue chromatographed on silica gel with 9:1 toluene:ethyl acetate as eluent to give product. Crystallization from toluene yields benzyl N-[3,5-dichloro-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamate, m.p. 164-6°.

Example 12

To 100 mg of N-[3,5-dimethyl-4-(4'-hydroxyphenoxy)-phenyl]oxamic acid in 20 ml ammonium hydroxide cooled in an ice bath is added 6.06 ml of .066M ethanolic bromine. After overnight stirring the solution is concentrated slightly and acidified with 2N hydrochloric acid. The solid is filtered off and recycled as above three more times. The final crude solid is crystallized from toluene to afford N-[3,5-dimethyl-4-(4'-hydroxy-3'-bromophenoxy)-phenyl]oxamic acid, m.p. 161-5° (dec.)

Example 13

To 250 mg of N-[3,5-dichloro-4-(4'-hydroxyphenoxy)-phenyl]oxamic acid in 20 ml ammonium hydroxide cooled in an ice bath is added 2.2 ml of .394M ethanolic iodine. When addition is complete, the solution is stirred at ambient for two hours, then concentrated slightly and filtered. The filtrate is acidified with 2N hydrochloric acid and twice extracted with ethyl acetate. The organic fractions are combined, dried, filtered, and stripped to give a solid which is crystallized from toluene to afford N-[3,5-dichloro-4-(4'-hydroxy-3'-iodophenoxy)-phenyl]oxamic acid, m.p. 218-20° (dec.)

Example 14

Methyl N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]-oxamate (1.74 g), 50 ml of dihydropyran, 1 ml dimethylformamide, and 3 drops of concentrated hydrochloric acid are stirred at room temperature overnight. Solvent is evaporated and the residue chromatographed on silica gel with 9:1 through 8:2 toluene:ethyl acetate as eluent to yield methyl N-{3,5-dimethyl-4-[3'-isopropyl-4'-(2"-tetrahydropyranyloxy)-phenoxy]-phenyl)-oxamate. NMR (CD_3OD): δ 1.2 (6H, d of d), 1.7 (6H,m), 2.1 (6H,s) 3.3 (1H,m), 3.5 (2H,m), 3.9(3H,s), 5.3 (1H,t), 6.4 (1H, d of d), 6.7 (1H,d), 7.0 (1H,d), 7.5 (2H,s)

Example 15

Methyl N-[3,5-dimethyl-4-(3'-isopropyl-4'-(2"-tetrahydropyranyloxy)-phenoxy)-phenyl]oxamate (1.23 g)

and 3.1 ml of 1.0N sodium hydroxide in 40 ml methanol are refluxed 30 min., then stirred at ambient temperature overnight. Solvent is evaporated, the residue dissolved in water, extracted with ether, chilled in an ice bath and neutralized with 3.1 ml 1.0N hydrochloric acid. The mixture is extracted twice with ethyl acetate and the combined organic fractions dried, filtered, and stripped, giving N-[3,5-dimethyl-4-(3'-isopropyl-4'-(2"-tetrahydropyranyloxy)-phenoxy)-phenyl] oxamic acid, m.p. 152-6° (dec.)

Example 16

Cholic acid (1.71 g), 1.50 g of methyl N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamate, 1.61 g of N-(dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, and 260 mg of N,N-dimethylaminopyridine are stirred in 150 ml tetrahydrofuran for 48 hours. Solvent is evaporated and the residue is redissolved in ethyl acetate and is washed with water then brine. Solvent is dried, filtered and stripped, and the residue is chromatographed on silica gel with ethyl acetate/ethanol to afford 4-{2,6-dimethyl-4-[(2-methoxy-1,2-dioxoethyl)amino]phenoxy}-2-isopropylphenyl 3,7,12-(3α,5β,7α,12α)-trihydroxycholan-24-oate.

Example 17

Cholic acid (1.79 g), 2.08 g of benzyl N-[3,5-dichloro-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamate, 1.68 g of N-(dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride and 270 mg of dimethylaminopyridine are stirred in 150 ml tetrahydrofuran for 18 hours. Solvent is evaporated and the residue is redissolved in ethyl acetate and extracted with water. The ethyl acetate is dried, filtered, and stripped and the residue chromatographed on silica gel with 20:80 through 10:90 toluene:ethyl acetate to afford 4-{4-[(2-benzyloxy-1,2-dioxoethyl)amino]-2,6-dichlorophenoxy}-2-isopropylphenyl 3,7,12(3α,5β,7α,12α-trihydroxycholan-24-oate, as an amorphous solid, m.p. 119-128°dec.

Example 18

4-{4-[(2-benzyloxy-1,2-dioxoethyl)amino]-2,6-dichlorophenoxy}-2-isopropylphenyl 3,7,12(3α,5β,7α,12α)-trihydroxycholan-24-oate (260 mg) and 26 mg of 10% palladium on carbon in 50 ml ethanol are treated with hydrogen on a Parr shaker. Catalyst is removed by filtering through Celite and the filtrate is stripped to give 4-{2,6-dichloro-4-[(2-hydroxy-1,2-dioxoethyl)amino]phenoxy}-2-isopropylphenyl 3,7,12-(3α,5β,7α12α)-trihydroxycholan-24-oate, as an amorphane monohydrate, m.p. 180-92° (dec.).

Example 19

A solution of 480 mg (137 mmol) of [5-(4-amino-2,6-dimethylphenoxy)-2-hydroxyphenyl](4-fluorophenyl)methanone in 5 ml of diethyl oxalate is heated at 100° for 2.5 hours. The excess diethyl oxalate is evaporated with a nitrogen stream and the residue is triturated with petroleum ether and filtered. The solid is dissolved in methylene chloride, the solution is filtered and the filtrate is evaporated to give ethyl N-[4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl] oxamate.

The starting material is prepared as follows:

To a solution of 26.0g (61.0 mmol) of 4,4'-dimethoxydiphenyliodonium tetrafluoroborate and 10.7 g (64.0 mmol) of 2,6-dimethyl-4-nitrophenol in 250 ml methylene chloride is added 0.5 g of copper powder and 10 ml (72.0 mmol) of triethylamine. The reaction mixture is stirred at room temperature for 6 days, then filtered. The filtrate is washed with 100 ml of 1N hydrochloric acid, 100 ml of water, dried ($CaSO_4$), filtered and evaporated. The residue is washed with ethanol to give 3,5-dimethyl-4-(4'-methoxyphenoxy)-nitrobenzene, m.p. 117-20°.

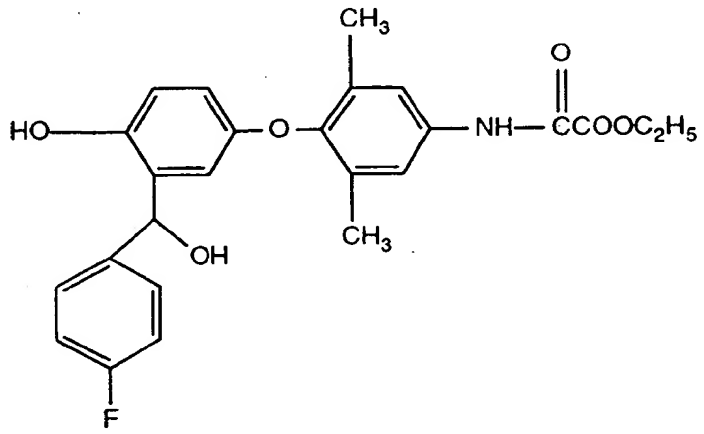
To a solution of 4.5 g (16.5 mmol) of 3,5-dimethyl-4-(4'-methoxyphenoxy)-nitrobenzene and 6.63 g (41.8 mmol) of p-fluorobenzoyl chloride in 100 ml methylene chloride is added 15.8 g (83.3 mmol) of titanium tetrachloride. The reaction mixture is stirred for 8 days at room temperature, then poured into ice water (300 ml) and stirred 2 hours. The organic layer is separated, washed with 5% aqueous sodium carbonate, water, dried ($CaSO_4$) and evaporated. The residue is triturated with ether-petroleum ether and recrystallized from methanol to give (4-fluorophenyl)[2-methoxy-5-(2,6-dimethyl-4-nitrophenoxy)phenyl]methanone, m.p. 167-168°.

A solution of 5.12 g (13.0 mmol) of (4-fluorophenyl)[2-methoxy-5-(2,6-dimethyl-4-nitrophenoxy)phenyl]methanone in 100 ml methylene chloride is chilled in an ice bath and 40 ml (40 mmol) of 1.0 M boron trichloride in methylene chloride is gradually added. The solution is stirred at room temperature overnight, then poured into 300 ml of ice water and stirred 2 hours. The organic layer is separated, washed with 5% aqueous sodium carbonate, water, dried ($CaSO_4$) and evaporated. The residue is recrystallized from ethanol to give (4-fluorophenyl)[2-hydroxy-5-(2,6-dimethyl-4 nitrophenoxy)phenyl]-methanone, m.p. 148-150°.

A solution of 2.77 g (7.3 mmol) of (4-fluorophenyl)[2-hydroxy-5-(2,6-dimethyl-4-nitrophenoxy)phenyl]methanone in 200 ml ethyl acetate with 1.0 g of 10% palladium on carbon is hydrogenated on a Parr apparatus for 2.5 hours at 50 psi and room temperature, then filtered and evaporated to give [5-(4-amino-2,6-dimethylphenoxy)-2-hydroxyphenyl]-(4-fluorophenyl)methanone.

Example 20

A slurry of Raney nickel (10 ml) is washed with water (3x25 ml), ethanol (2x25 ml) and added to a solution of 1.4 g (3.1 mmol) of ethyl N-[4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl] oxamate in 20 ml ethyl acetate diluted with 80 ml ethanol. The reaction mixture is hydrogenated on a Parr apparatus for 2 hours at 45 psi and room temperature, then filtered and evaporated. The residue is recrystallized from ether-petroleum ether to give ethyl N-[4-[3'-[(4-fluorophenyl) hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate, m.p. 146-148°.



Example 21

A solution of 900 mg (2.0 mmol) of ethyl N-[4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl] oxamate in 20 ml of ethanol and 2.5 ml (2.5 mmol) of 1.0 N aqueous sodium hydroxide is refluxed 2 hours, then evaporated. The residue is dissolved in water and the aqueous solution is washed with ethyl acetate, acidified with 6 N aqueous hydrochloric acid and extracted with ether. The ether layer is washed with water, dried ($CaSO_4$) and evaporated. Recrystallization from methylene chloride - petroleum ether gives N-[4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethyl-phenyl]oxamic acid, m.p. 160-162° dec.

Example 22

The following compounds are prepared using essentially the same procedure as described in the above examples for N-[4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid, via the corresponding ethyl ester.

(a) N-[3,5-dichloro-4-[3'-[(4-fluorobenzoyl)]-4'-hydroxyphenoxy]phenyl]oxamic acid, m.p. 196°;
(b) N-[3,5-dichloro-4-[3'-(4-chlorobenzoyl)-4'-hydroxyphenoxy]phenyl] oxamic acid, m.p. 199°;
(c) N-[4-[3'-(4-chlorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl] oxamic acid, m.p. 188°;
(d) N-[3,5-dichloro-4-[4'-hydroxy-3'-(1-oxobutyl)phenoxy]phenyl] oxamic acid, m.p. 183°;
(e) N-[4-[3'-(benzoyl)-4'-hydroxyphenoxy]-3,5-dimethyl-phenyl]oxamic acid.

Example 23

To a solution of 300 mg (0.71 mmol) of N-[4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl] oxamic acid in 10 ml methanol is added 130 mg (3.5 mmol) of sodium borohydride. The reaction mixture is stirred at room temperature for 15 minutes, then diluted with water, acidified with 6 N aqueous hydrochloric acid and extracted with ether. The ether layer is washed with water, dried ($CaSO_4$) and evaporated. The residue is taken up in methylene chloride, filtered and evaporated. Recrystallization from methylene chloride-petroleum ether gives N-[4-[3'-[(4-fluorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl] oxamic

acid, m.p. 142-147° dec.

Example 24

The following compounds are prepared using essentially the same procedure as described above for N-[4-[3'-(4-fluorophenyl) hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid.

(a) N-[3,5-dichloro-4-[3'-[(4-chlorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-phenyl]oxamic acid, m.p. 155°;

(b) N-[4-[3'-[(4-chlorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethyl-phenyl]oxamic acid, m.p. 123°.

Example 25

A solution of 660 mg (1.96 mmol) of 4-(4-amino-2,6-dimethylphenoxy)-2-[(4-fluorophenyl)methyl]phenol in 5 ml diethyl oxalate is heated at 100° for 1.25 hours. The excess diethyl oxalate is evaporated with a nitrogen stream and the residue is triturated with petroleum ether and filtered. Flash chromatography gives ethyl N-[4-[3'-[(4-fluorophenyl)methyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate, m.p. 153-156°.

The starting material is prepared as follows:

To a solution of 2.2 g (5.55 mmol) of (4-fluorophenyl)[2-methoxy-5-(2,6-dimethyl-4-nitrophenoxy)phenyl]methanone in 10 ml methylene chloride and 3 ml trifluoroacetic acid is added 2.1 g (18.0 mmol) of triethylsilane. The solution is stirred overnight at room temperature, then diluted with ether (100 ml) and washed with water, 5% aqueous sodium carbonate, water, dried ($CaSO_4$) and evaporated. The residual oil is flash chromatographed to give 1-[(4-fluorophenyl)methyl]-2-methoxy-5-(2,6-dimethyl-4-nitrophenoxy)benzene, m.p. 105-110°.

To a solution of 1.7 g (4.5 mmol) of 1-[(4-fluorophenyl)methyl]-2-methoxy-5-(2,6-dimethyl-4-nitrophenoxy)benzene in 100 ml methylene chloride is added 13.5 ml (13.5 mmol) 1.0 N boron tribromide in methylene chloride. The solution is stirred overnight at room temperature, poured into ice water (300 ml) and stirred 1 hour. The organic layer is separated, washed with water, dried ($CaSO_4$) and evaporated. Flash chromatography of the residue gives 2-[(4-fluorophenyl)methyl]-4-(2,6-dimethyl-4-nitrophenoxy)phenol, m.p. 127-132°.

A slurry of Raney nickel (10 ml) is washed with water (2 x 25 ml), ethanol (2 x 25 ml) and added to a solution of 2-[(4-fluorophenyl)methyl]-4-(2,6-dimethyl-4-nitrophenoxy)phenol in 100 ml ethanol. The reaction mixture is hydrogenated on a Parr apparatus for 1.5 hours at 45 psi and room temperature, filtered and evaporated. Recrystallization from ether-petroleum ether gives 4-(4-amino-2,6-dimethylphenoxy)-2-[(4-fluorophenyl)methyl]phenol, m.p. 179-182°.

Example 26

A solution of 440 mg (1.0 mmol) of ethyl N-[4-[3'-[(4-fluorophenyl) methyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl] oxamate in 20 ml ethanol and 1.2 ml (1.2 mmol) 1.0 N aqueous sodium hydroxide is refluxed for 1 hour, then evaporated. The residue is dissolved in water, and the solution is washed with ether, acidified with 6 N aqueous hydrochloric acid and extracted with ether. The ether layer is washed with water, dried ($CaSO_4$) and evaporated. The residue is recrystallized from methylene chloride to give N-[4-[3'-(4-fluorophenyl)methyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid, m.p. 182-184° dec.

Example 27

The following examples are prepared using essentially the same procedure as described above for N-[4-[3'-(4-fluorophenyl)methyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid.

(a) N-[3,5-dichloro-4-[3'-[(4-fluorophenyl)methyl]-4'-hydroxyphenoxy]phenyl]oxamic acid, m.p. 180°;

(b) N-[3,5-dichloro-4-[3'-[(4-chlorophenyl)methyl]-4'-hydroxyphenoxy]phenyl]oxamic acid, m.p. 185°;

(c) N-[4-[4'-hydroxy-3'-(phenylmethyl)phenoxy]-3,5-dimethylphenyl]oxamic acid, m.p. 154°;

(d) N-[4-[3'-[(4-chlorophenyl)methyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamic acid, m.p. 155°.

Example 28

3,5-Dimethyl-4-(3'-isopropylphenoxy)-nitrobenzene (5.21 g) and 521 mg of 10% platinum on carbon in 150 ml ethanol are reduced under hydrogen on a Parr shaker. The solution is filtered through Celite to remove catalyst and the filtrate is stripped to give 3,5-dimethyl-4-(3'-isopropylphenoxy)-aniline which is then fused with

50 g of dimethyl oxalate at 120° for four hours. The resulting mixture is concentrated under high vacuum and the residue chromatographed on silica gel with 9:1 toluene:ethyl acetate as eluent to yield methyl N-[3,5-dimethyl-4-(3'-isopropylphenoxy)-phenyl]oxamate; NMR ($CDCl_3$): δ 1.2 (6H, d), 2.1 (6H, s), 2.8 (1H, m), 4.0 (3H, s), 6.5 (1H, d of d), 6.7 (1H, t), 6.9 (1H, d of d), 7.2 (1H,t), 7.4 (2H, s); 8.8 (1h, br s).

The starting material is prepared by reaction of 3-isopropyl-phenol with 4-chloro-3,5-dimethylnitrobenzene using methodology described in example 1.

Example 29

3,5-Dimethyl-4-(3'-isopropyl-4'-hydroxyphenoxy)-aniline (1.65 kg, 6.08 mol) is suspended in diethyl oxalate (8.5 L) and heated to an internal temperature of 100°. At 85° a complete solution is obtained. After 3 hours at 100° the reaction is complete. On cooling to 50° the solution is diluted with heptane (8 L) and the mixture is cooled to 5°. The solids are collected by filtration and the filter cake is washed with heptane (3 X 200 mL). After drying overnight (50°, 1 Torr) the material is dissolved in hot ethyl acetate (12 L). This solution is diluted with heptane (12 L) and the mixture is cooled to 10° for 1 hour and filtered. The filter cake is washed with heptane (2 X 1 L) and then dried for 72 hours (60°, 0.5 Torr) to obtain ethyl N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamate, m.p. 170-171°.

The starting material is prepared as follows:

2-Isopropylphenol (5.0 kg, 36.7 mol) is dissolved in ethyl acetate (20.8 L) and to this is added triethylamine (4.48 kg, 44.1 mol). This solution is cooled to -12° and to this is added acetyl chloride (3.15 kg, 40.2 mol) over a period of 2.5 hours keeping the temperature below -10°. Triethylamine hydrochloride precipitates immediately. After the addition is complete stirring is continued for 1 hour at 15° at which time a solid mass is formed. This is dissolved by the addition of water (12L). After separation of the layers the organic layer is further washed with water (2 X 12L) and evaporated in vacuo (50°, 2 Torr) and then at 70°, 2 Torr to give 2-isopropyl-phenyl acetate as a residual amber oil.

2-Isopropyl-phenyl acetate (3.24 kg, 18.2 mol) is dissolved in nitrobenzene (12.5 L). After cooling this solution to 100, aluminum chloride (6.0 kg/ 45.0 mol) is added in portions, keeping the temperature at approximately 20°. After the addition is complete the reaction mixture is heated at 35° for 18 hours. After cooling to room temperature this mixture is poured onto hydrochloric acid (1.0 N, 16.5 L), keeping the temperature between 20-25° with ice-cooling. Stirring is continued for 15 minutes after the addition is complete. At this time the solids are collected by filtration and washed with water (20 L). This material is combined with that of a run of exactly the same size and dissolved in methanol (16L). To this solution is added charcoal (100 g) and after stirring for 30 minutes this mixture is filtered. To this decolorized solution water (18 L) is slowly added to precipitate the product. At this time the mixture is cooled to 4°C for 1 hour and the solids are collected by filtration, washed with hexane (4 X 2 L) to remove residual nitrobenzene and dried in vacuo (50°C, 1 Torr) for 18 hours to obtain 4-acetyl-2-isopropylphenol, m.p. 142-144°.

4-Acetyl-2-isopropylphenol (3.69 kg, 20.7 mol) is dissolved in dimethylformamide (14 L). To this solution is then added powdered anhydrous potassium carbonate (3.16 kg, 22.8 mol), anhydrous potassium iodide (369 g, 2.22 mol) and benzyl chloride (2.88 kg, 22.8 mol). This mixture is then heated to 80° for 2 hours, cooled to 50° and diluted with water (46 L). After cooling to 5° the mixture is stirred for 1 hour and the solids are collected by filtration and washed with water (20 L). After air drying overnight, the solids are dissolved in methanol (16 L) at 50° and filtered into a 20 gallon container. The filtrate is diluted with water (10 L) over a period of 20 minutes at 40°. After the addition is complete the mixtue is stirred for 1 hour at 5° and the solids are filtered and dried in vacuo (80°, 15 Torr) for 5 days to obtain 4-benzyloxy-3-isopropylacetophenone, m.p. 55-56°.

4-Benzyloxy-3-isopropylacetophenone (5.50 kg, 20.5 mol) is dissolved in acetic acid (25 L). To this solution is added anhydrous sodium acetate (502 g, 6.10 mol) with stirring which is continued until complete solution is obtained at 200. At this time peracetic acid (35%, 8.90 kg, 40.1 mol) is added all at once. At first the temperature drops to 14° and then a slow exotherm occurs with the temperature rising from 14-32° over a period of 5 hours. The exotherm is controlled by a cold water bath. After stirring overnight at room temperature, the solution is cooled to 15° and a solution of sodium sulfite (4.5 kg, 35.7 mol) in water (20 L) is added slowly, keeping the temperature below 200. When all the solution is added, a negative starch/iodide reaction is obtained. The mixture is extracted with toluene (3 X 10 L) and the combined extracts are washed with water (4 X 12 L). Distillation of the toluene in vacuo (50°, 3 Torr) gives 4-benzyloxy-3-isopropylphenyl acetate as an amber oil.

4-Benzyloxy-3-isopropylphenyl acetate (5.59 kg, 19.7 mol) is added to a solution of sodium hydroxide (1.20 kg, 30.0 mol) in a mixture of water (30 L) and methanol (30 L). This solution is stirred at 24° for 1 hour. A black-colored solution develops. This is concentrated in vacuo (40°, 3 Torr) to remove the methanol. This residue is then extracted with ethyl acetate (2 X 16 L) and the combined organic layers are washed with aqueous sodium hydroxide (1 N, 2 X 10 L) and water (3 X 12 L). The solvent is stripped in vacuo (50°, 3 Torr) to yield an amber

oil. This oil is then triturted with heptane (10 L) for 4 hours and the allowed to stand overnight at room temperature at which time the solids are collected by filtration and washed with cold heptane (2 X 1 L). After air-drying, the product is further dried in vacuo (25°, 120 Torr) for 72 hours to give 4-benzyloxy-3-isopropylphenol as a low melting solid, m.p. 39-40°.

A suspension of 4-nitro-2,6-dimethylphenol (2.68 kg, 16.1 mol) in dichloromethane (30 L) is cooled to -15°. To this is added pyridine (3.17 kg, 19.5 mol) all at once to obtain a black solution. Triflic anhydride (5.50 kg, 19.5 mol) is then added over a period of 2 hours, keeping the temperature between -10° and -5°. After the addition is complete stirring is continued for 2.5 hours at -3°. At this time cold water (3°, 24 L) is added dissolving the black suspension. After separation of the layers the organic layer is washed with hydrochloric acid (1 N, 12 L), water (2 X 12 L), aqueous sodium hydroxide (2 X 12 L) and water (4 X 12 L). All the aqueous washes are kept cold (3°) and the batch temperature at this time is approximately 5° throughout. After drying over magnesium sulfate (5.0 kg), the organic layer is filtered and evaporated in vacuo at 40°. The residue is dissolved in heptane (4 L) and the dark solution is stirred and seeded to initiate crystallization. After standing overnight at 4° the solids are collected by filtration and washed with heptane (2 X 500 mL). After drying in vacuo (24°, 120 Torr) for 24 hours 4-nitro-2,6-dimethylphenyl trifluoromethanesulfonate is obtained as a brownish solid, m.p. 64-66°.

4-Nitro-2,6-dimethylphenyl trifluoromethanesulfonate (4.06 kg, 13.6 mol) is dissolved in anhydrous N-methylpyrrolidinone (42 L) and to this solution is added anhydrous lithium chloride (900 g) all at once. The internal temperature is raised to 120° at which time the color changes to a dark golden brown. After 10 hours at this temperature the color of the solution is dark brown. The reaction is then cooled to 5° and diluted with cold water (5°, 21 L) at such a rate as to keep the temperature below 150. Afte the addition is complete the mixture is stirred for 1 hour at 5°. The product is collected by filtration and washed with water (4 X 1 L). This dark brown solid is dissolved in t-butyl methyl ether (42 L) and stirred first with charcoal and then anhydrous magnesium sulfate (10 pounds). After filtration the solvents are removed in vacuo (40°, 3 Torr) to obtain a tan solid which is dried in vacuo (25°, 3 Torr) for 2 days to obtain 4-chloro-3,5-dimethylnitrobenzene, m.p. 101-105°.

Powdered anhydrous potassium carbonate (1.95 kg, 14.1 mol) is suspended in anhydrous dimethyl sulfoxide (20 L) and to this suspension is added 4-benzyloxy-3-isopropyl-phenylacetate (2.36 kg, 9.74 mol) and 4-chloro-3,5-dimethylnitrobenzene (1.81 kg, 9.74 mol). This mixture is heated to an internal temperature of 125° for 23 hours. After cooling to 40° the reaction mixture is diluted with ice water (40 L). The precipitate is filtered, washed with water 5 x 4 L) and air-dried for 48 hours to obtain partially wet brown solids. The product is dissolved in hot isopropanol (4 L) and to this refluxing solution is added charcoal (KB, 200 g). After stirring at reflux for 0.5 hour, the mixture is filtered hot and the filtrate is cooled to 10° for 1 hour. The solids are collected by filtration and washed with cold (4°) isopropanol (3 x 500 mL). After drying overnight (25°, 3 Torr) the product is subjected to crystallization from isopropanol (3 L) to obtain 3,5-dimethyl-4-(3'-isopropyl-4'-benzyloxyphenoxy)-nitrobenzene, m.p. 99-100°.

3,5-Dimethyl-4-(3'-isopropyl-4'-benzyloxyphenoxy)-nitrobenzene, (2.86 kg, 7.31 mol) is dissolved in a mixture of ethanol/tetrahydrofuran (10:1, 114L) and cooled to 100. This is admixed with 10% Pd/C (800g) and the system is pressurized to 15 psi with hydrogen gas. The hydrogenation is continued for 18 hours. The mixture is then filtered through Celite and the Celite is washed with tetrahydrofuran (30 L). The filtrate is then evaporated in vacuo to dryness (50°, 3 Torr). The solid residue is triturated with heptane (3L) and filtered. The filter cake is washed with heptane (2 X 500 mL) to obtain crude product which is then dissolved in hot ethyl acetate (14 L) and diluted with heptane (30 L). The product slowly precipitates and the mixture is cooled at 10° for 1 hour, collected by filtration and washed with ethyl acetate/hexane 1:2 (2 X 500 mL). The filter cake is then dried (60°, 3 Torr) for 24 hours to yield 3,5-dimethyl-4-(3'-isopropyl-4'-hydroxyphenoxy)-aniline, m.p. 180-181°.

Example 30

Ethyl N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamate (1.59 kg, 4.2 mol) is suspended in aqueous sodium hydroxide solution (1.0 N, 12 L) at room temperature (24°). After stirring at this temperature for 4 hours a bluish solution is obtained. This is filtered to remove some sediment and the filtrate is added slowly to a solution of hydrochloric acid (12 N, 1.4 L) in methanol (8 L), precipitating a solid. The slurry is stirred for 1 hour and the solids are collected by filtration, washed with water (4 X 500 mL) and dried overnight (60°, 2 Torr) to obtain crude acid, mp 185° dec. This is dissolved in ethyl acetate (6.5 L) at room temperature and to this solution is added charcoal (KB, 100 g). After stirring for 0.5 hour, the mixture is filtered and diluted with heptane (16.3L). After stirring at room temperature for 2 hours, the solids are collected by filtration, washed with ethyl acetate/heptane (1:2.5, 2 X 500 mL) and dried overnight (65°, 0.5 Torr) to yield product, m.p. 187°. This material is dissolved in hot acetonitrile (4 L) and to this is added HPLC grade water (12 L) slowly, keeping the temperature at 60° until the addition is complete. The solution is allowed to crystallize slowly at 50° and

after initiation of the crystallization, cooling is slowly applied and then the mixture is kept at 10° for 1 hour. The product is collected by filtration, washed with acetonitrile/water (1:4, 2 X 500 mL) and dried invacuo (70°, 0.5 Torr) for 24 hours. The material is then sieved and redried for 48 hours (70°, 0.5 Torr) to obtain N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamic acid, m.p. 187-188°.

Example 31

[5-(4-Amino-2,6-dimethylphenoxy)-2-hydroxyphenyl](4-fluorophenyl)methanone (48g. 0.13 mol) and diethyl oxalate (99.7 gm, 0.6 mol) are combined and heated with stirring under a nitrogen atomosphere at 100° for 10 hours. The reaction is stirred to room temperature overnight and the resulting suspension trituarated with heptane (300 ml). The product is filtered, washed with heptane (3 X 100 ml) and dried in vacuo at 60°/3 mmHg to give ethyl N-[4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]3,5-dimethylphenyl]oxamate, m.p. 150-152°.

The starting material is prepared as follows:

A mixture of dimethylsulfoxide (875 ml), p-methoxyphenol (43.3g 0.3 48 mol), powdered potassium carbonate (69.9 g, .5 mol) and 4-chloro-3,5-dimethylnitrobenzene (see example **30**, 64.6 g; 0.348 mol) is heated at a temperature of 125° for 18 hours. The suspension is cooled to 25° and pumped onto ice water (2620ml) with stirring. The mixture is stirred for 2 hours, the product is filtered, washed with water (4X300 ml) and air dried. A solution of the product in tert-butylmethyl ether (3L) is dried over magnesium sulfate and treated with charcoal (6.4g) for 2.5 hours. The drying agent is filtered off and the filtrate concentrated in vacuo at 50°/3mm Hg to give product which is recrystallized from toluene (212ml) and petroleum ether (600 ml) to give 3,5-dimethyl-4-(4'-methoxyphenoxy)nitrobenzene, m.p. 120-123°.

The above nitrobenzene derivative is then converted to (4-fluorophenyl)[2-hydroxy-5-(2,6-dimethyl-4-nitrophenoxy)phenoxy)phenyl]methanone similarly to procedures described in example **20**.

(4-Fluorophenyl) [2-hydroxy-5-(2,6-dimethyl-4-nitrophenoxy)phenyl]methanone (62.8g, 0.16 mol) is dissolved in ethyl acetate (4L) and hydrogenated at atmospheric pressure over 5% platinum on carbon (13.2g). When the theoretical amount of hydrogen is consumed, the hydrogenation is stopped, the catalyst is filtered off, and the ethyl acetate solution is concentrated to dryness at 50°/3mm Hg. The residue is triturated hot with isopropanol (1L) and collected to yield [5-(4-amino-2,6-dimethylphenoxy)-2-hydroxyphenyl](4-fluorophenyl)methanone, m.p. 198-202°.

Example 32

To a stirred suspension of sodium borohydride (5.42g, 0.14 mol) in tetrahydrofuran (310 ml) at 0° under a nitrogen atmosphere is added acetic acid (17.3 gm, .29 mol) over 1 hour. The cooling bath is removed and the suspension is stirred at 24°. Ethyl N-[4-[3'-(4-fluorobenzoyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate (60.3g, 0.13 mol) is added portionwise to the suspension over 5 minutes. The solution is stirred for 3 hours at 24°. The reaction is cooled to 10° and water (604 ml) is added. The pH is adjusted to 5-7 with a saturated sodium bicarbonate solution (180 ml). The product is extracted with ether (3 X 1L), washed with brine (1L), dried over sodium sulfate, filtered and concentrated at 50°/3 mm Hg to give crude product. A solution of the crude product in ethyl acetate (50 ml) is passed over a column of Kiesel gel 60 (23-400 mesh) using a mixture of ethyl acetate (7.5L) and heptane (2.5L) as the eluent.

The resulting product is dissolved in ethyl acetate (1.1L), treated with charcoal (12g), filtered and concentrated in vacuo to give a foam. The foam is dissolved in 470 ml of ethyl acetate and crystallized out with the addition of heptane (660 ml). The mixtue is stirred for 48 hours and the product is filtered, washed with a mixture of heptane (20 ml) and ethyl acetate (10 ml) and dried in vacuo at 60°/3 mmHg to give ethyl N-[4-[3'-[(4-fluorophenyl) hydroxymethyl]-4'-hydroxyphenoxy]3,5-dimethylphenyl]oxamate, m.p. 148-150°.

Example 33

The following compounds are prepared using procedures similar to those described herein:

(a) ethyl N-[3,5-dichloro-4-[3'-[(4-chlorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]phenyl]oxamate;

(b) ethyl N-[4-[3'-[(4-chlorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate;

(c) ethyl N-4-[3'-(phenyl-hydroxymethyl)-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate;

(d) ethyl N-[4-[3'-[(4-tolyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethyl- phenyl]oxamate;

(e) ethyl N-[4-[3'-[(4-fluorophenyl)hydroxymethyl]-4'-methoxyphenoxy]-3,5-dimethylphenyl]oxamate, m.p. 155-156°.

Example 34

Ethyl N-[4-[3'-[(4-fluorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate according to Example 20 is resolved by high pressure liqid chromatography (HPLC) on a chiral OD (Daicel) column (cellulose para-methylbenzoate coated on silca gel) eluting with 80:20 hexane/ethanol to give isomer A (retention time 115 minutes), α_D = + 23,1°C (C= 0.64 in acetonitrile), m.p. 150-152°C; and isomer B (retention time 150 minutes), α_D = -21.7°C (C= 0.47 in acetonitrile), m.p. 147-150°C.

Example 35

Preparation of 10,000 tablets each containing 0.2 mg of the active ingredient, for example, N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]oxamic acid,

Active ingredient	2.00 g
Lactose	2,535.00g
Corn starch	125.00g
Polyethylene glycol 6,000	15.000g
Magnesium stearate	40.00g
Purified water	q.s.

Procedure:

All the powders are passed through a screen with openings of 0.6 mm. The drug substance, lactose, magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 65 ml of water and the suspension added to the boiling solution of the polyethylene glycol in 250 ml of water. The paste formed is added to the powders, which are granulated, if necessary, with an additional amount of water. The granulate is dried ovenight at 35°C broken on a screen with 1.2 mm openings and compressed into tablets, using concave punches uppers bisected.

Analogously tablets are prepared, containing about 0.01-10 mg of one of the other compounds disclosed and exemplified herein.

Example 36

Preparation of 1,000 capsules each containing 0.05 mg of the active ingredient, for example, ethyl N-[4-[3'-[(4-fluorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate

Active ingredient	0.05g
Lactose	217.00g
Modified starch	80.00g
Magnesium stearate	3.00g

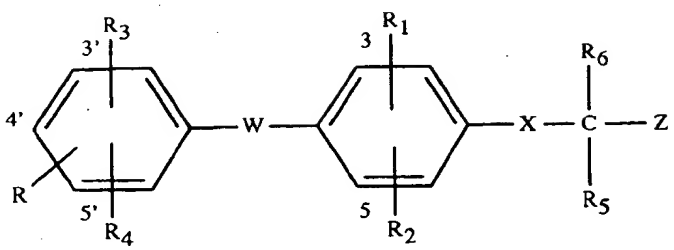
Procedure:

All the powders are passed through a screen with openings of 0.6 mm. The drug substance is placed in a suitable mixer and mixed first with the magnesium stearate, then with the lactose and starch until homogenous. No. 2 hard gelatin capsules are filled with 300 mg of said mixture each, using a capsule filling machine.

Analogously capsules are prepared, containing about 0.01-10 mg of the other compounds disclosed and exemplified herein.

Claims

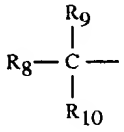
1. A compound of the formula



(I)

wherein

R is hydrogen, hydroxy, esterified hydroxy or etherified hydroxy;
R_1 is hydrogen, halogen, trifluoromethyl or lower alkyl;
R_2 is hydrogen, halogen, trifluoromethyl or lower alkyl;
R_3 is halogen, trifluoromethyl, lower alkyl, aryl, aryl-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl;
or
R_3 is the radical

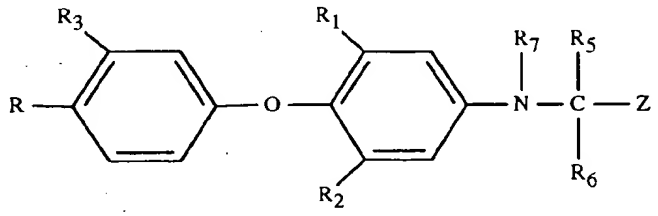


wherein R_8 is hydrogen, lower alkyl, aryl, cycloalkyl, aryl-lower alkyl or cycloalkyl-lower alkyl; R_9 is hydroxy or acyloxy; R_{10} represents hydrogen or lower alkyl; or R_9 and R_{10} together represent oxo;
R_4 is hydrogen, halogen, trifluoromethyl or lower alkyl;
X is $-NR_7$;
W is O or S;
R_5 and R_6 together represent oxo;
R_7 represents hydrogen or lower alkyl;
Z represents carboxyl, carboxyl derivatized as a pharmaceutically acceptable ester or as a pharmaceutically acceptable amide; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R is located at the 4'-position, R_1 and R_2 are located at the 3 and 5 positions, and R_3 and R_4 are located at the 3' and 5'-positions.

3. A compound according to claim 1 wherein W represents O.

4. A compound according to claim 1 of the formula

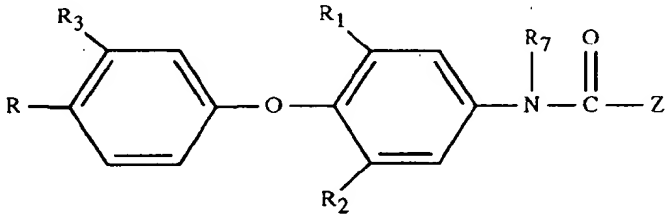


(II)

wherein R is hydroxy, esterified hydroxy or etherified hydroxy; R_1 and R_2 independently represent hydrogen, halogen, trifluoromethyl or C_1-C_3alkyl; R_3 represents lower alkyl, lower alkanoyl, hydroxy-lower alkyl, carbocyclic arylmethyl, carbocyclic aroyl or carbocyclic aryl-hydroxymethyl; R_5 and R_6 together represent

oxo; R_7 represents hydrogen or lower alkyl; and Z represents carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester or amide; or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 1 of the formula



(III)

wherein R is hydroxy, esterified hydroxy or etherified hydroxy; R1 represents hydrogen, halogen, trifluoromethyl or C_1-C_3alkyl; R_2 represents halogen, trifluoromethyl or C_1-C_3alkyl; R_3 represents lower alkyl, carbocyclic aroyl, carbocyclic arylmethyl or carbocyclic aryl-hydroxymethyl; R_7 represents hydrogen or lower alkyl; Z represents carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 5 wherein R represents hydroxy, acyloxy, lower alkoxy or tetrahydropyranyloxy.

7. A compound according to claim 5 wherein R is hydroxy, lower alkanoyloxy, lower alkoxy or tetrahydropyranyloxy; R_1 and R_2 represent halo or C_1-C_3-alkyl; R_3 is C_1-C_3-alkyl or monocyclic carbocyclic arylmethyl; R_7 is hydrogen or C_1-C_2-alkyl; Z is carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 5 wherein Z is carboxyl or carboxyl esterified as a pharmaceutically acceptable ester.

9. A compound according to claim 5 wherein R_1 and R_2 represent chloro or methyl; R_3 is isopropyl, benzyl or benzyl substituted by halogen, lower alkyl, lower alkoxy or trifluoromethyl; R_7 is hydrogen; Z is carboxyl or lower alkoxycarbonyl; or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 5 wherein R is hydroxy, lower alkanoyloxy, lower alkoxy or tetrahydropyranyloxy; R_1 and R_2 represent halo or C_1-C_3-alkyl; R_3 is carbocyclic aroyl or carbocyclic aryl-hydroxymethyl; R_7 is hydrogen or C_1-C_2-alkyl; Z is carboxyl or carboxyl derivatized as a pharmaceutically acceptable ester or amide; or a pharmaceutically acceptable salt thereof.

11. A compound according to any one of claims 1-10 wherein Z represents carboxyl or lower-alkoxycarbonyl.

12. A compound according to claim 5 wherein R is hydroxy; R_1 and R_2 are identical and represent C_1-C_3-alkyl or halogen; R_3 represents (a) phenyl-hydroxymethyl or phenyl-hydroxymethyl substituted on phenyl by halogen, lower alkyl, lower alkoxy or trifluoromethyl; or (b) benzoyl or benzoyl substituted by halogen, lower alkyl, lower alkoxy or trifluoromethyl; or (c) C_1-C_3-alkyl; R_7 is hydrogen; and Z represents carboxy or C_1-C_4-alkoxy-carbonyl; or a pharmaceutically acceptable salt thereof.

13. A compound according to claim 5 wherein R is hydroxy; R_1 and R_2 are identical and represent C_1-C_3-alkyl or halogen; R_3 represents (a) phenyl-hydroxymethyl substituted on phenyl by halogen; or (b) benzoyl substituted by halogen; or (c) C_1-C_3-alkyl; R_7 is hydrogen; and Z represents carboxy or C_1-C_4-alkoxy-carbonyl; or a pharmaceutically acceptable salt thereof.

14. A compound according to claim 5 wherein R is hydroxy; R_1 and R_2 represent chloro or methyl; R_3 is phenyl-hydroxymethyl or phenyl-hydroxymethyl substituted on phenyl by halogen, lower alkyl, lower alkoxy or trifluoromethyl; R_7 is hydrogen; Z is carboxyl or lower alkoxycarbonyl; or a pharmaceutically acceptable salt thereof.

15. A compound according to claim 5 wherein R is hydroxy; R_1 and R_2 are identical and represent C_1-C_3-alkyl

or halogen; R_3 is (a) 4-halo-phenyl-hydroxymethyl; or (b) C1-C_3 -alkyl; R_7 is hydrogen; and Z represents carboxy or C_1-C_4-alkoxy-carbonyl; or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 15 selected from the group consisting of
N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]-oxamic acid or a pharmaceutically acceptable salt thereof;
N-[3,5-dichloro-4-(4'-hydroxy-3' -isopropylphenoxy)-phenyl]-oxamic acid or a pharma- ceutically acceptable salt thereof;
ethyl N-[4-[3'-[(4-fluorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate; and
N-[4-[3'-[(4-fluorophenyl)hydroxymethyl]-4'-hydroxyphenoxy]-3,5-dimethylphenyl] oxamic acid or a pharmaceutically acceptable salt thereof.

17. A compound according to any one of claims 1-16 in form of a substantially pure optical isomer.

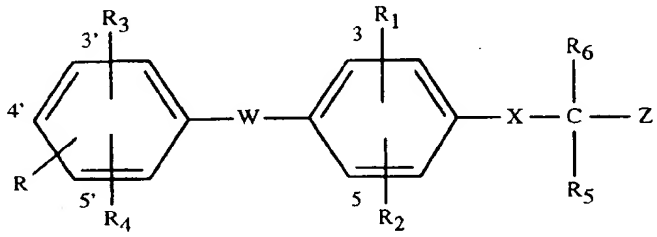
18. A compound according to any one of claims 1 to 17 for use in the prophylactic or therapeutic treatment of the human or animal body.

19. A pharmaceutical composition comprising an effective amount of a compound of any one of claims 1-18 in combination with one or more pharmaceutically acceptable carriers.

20. A cholesterol-lowering pharmaceutical composition according to claim 19.

21. Use of a compound according to any one of claims 1 to 18 or a pharmaceutically acceptable salt thereof; for the manufacture of a cholesterol-lowering pharmaceutical composition.

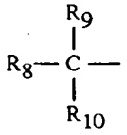
22. A process for the manufacture of a compound of formula I



(I)

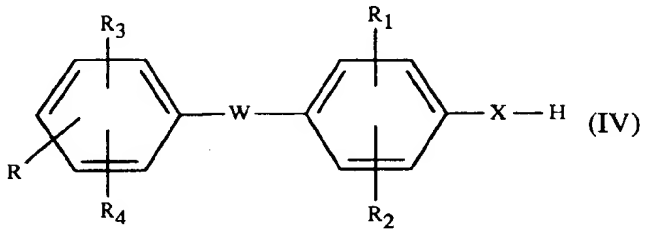
wherein

R is hydrogen, hydroxy, esterified hydroxy or etherified hydroxy;
R_1 is hydrogen, halogen, trifluoromethyl or lower alkyl;
R_2 is hydrogen, halogen, trifluoromethyl or lower alkyl;
R_3 is hydrogen, halogen, trifluoromethyl, lower alkyl, aryl, aryl-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl; or
R_3 is the radical



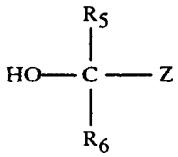
wherein R_8 is hydrogen, lower alkyl, aryl, cycloalkyl, aryl-lower alkyl or cycloalkyl-lower alkyl; R_9 is hydroxy or acyloxy; R_{10} represents hydrogen or lower alkyl; or R_9 and R_{10} together represent oxo;
R_4 is hydrogen, halogen, trifluoromethyl or lower alkyl;
X is -NR_7;
W is O or S;
R_5 and R_6 together represent oxo;
R_7 represents hydrogen or lower alkyl;
Z represents carboxyl, carboxyl derivatized as a pharmaceutically acceptable ester or as a phar-

maceutically acceptable amide; or of a pharmaceutically acceptable salt thereof; comprising condensing a compound of the formula



(IV)

wherein R, R_1-R_4, W and X have meaning as defined hereinabove, advantageously with a reactive functional derivative of a compound of the formula V



(V)

wherein R_5, R_6 and Z have meaning as defined hereinabove, in protected form as required; and in above said process, if temporarily protecting any interfering reactive group(s), removing said protecting group(s), and then isolating the resulting compound of the invention; and, if desired, converting any resulting compound of the invention into another compound of the invention; and/or, if desired, converting a free carboxylic function into a pharmaceutically acceptable ester or amide derivative, or converting a resulting ester or amide into the free acid or into another ester or amide derivative; and/or, if desired, converting a resulting free compound into a salt or a resulting salt into the free compound or into another salt, and/or, if desired, separating a mixture of isomers or racemates obtained into the single isomers or racemates, and/or, if desired, resolving a racemate obtained into the optical antipodes.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 81 0495

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
A	US-A-4 061 791 (C.M. HALL) * claims *	1-22	C07C233/56 A61K31/225
A	US-A-4 154 961 (J.H. SELLSTEDT ET AL.) * claims *	1-22	
A	EP-A-0 138 757 (CIBA-GEIGY AG) * claims *	1-22	
A	JOURNAL OF MEDICINAL CHEMISTRY vol. 18, no. 9 , 1975 , WASHINGTON US pages 926 - 933 J.H. SELLSTEDT ET AL. 'OXANILIC ACIDS, A NEW SERIES OF ORALLY ACTIVE ANTIALLERGIC AGENTS' * page 928 *	1-22	

TECHNICAL FIELDS SEARCHED (Int.Cl.5)

C07C
C07J

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	24 November 1993	Sanchez y Garcia,J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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L : document cited for other reasons

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